Received: 5 February 2025 | Accepted: 19 October 2025

DOI: 10.1002/jpn3.70275

JPGN

CONSENSUS STATEMENT

Gastroenterology: Inflammatory Bowel Disease

Reshaping study design for faster extrapolation-based drug approval in pediatric inflammatory bowel diseases: An ESPGHAN–NASPGHAN position paper

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Funding information

None

Abstract

Children with inflammatory bowel diseases (IBD) have limited access to the available advanced therapies, given the lengthy gap between adult and pediatric approval. We aimed to review key hurdles for pediatric trials and recommend practical solutions. This position paper was developed jointly by the European and North American Societies for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN and NASPGHAN), in consultation with patient representatives. A systematic review was performed for identified topics, and two voting rounds with two group meetings led to agreement on 24 statements. The systematic review (reviewing 4366 manuscripts, of which 123 were included in tables of evidence and 213 in support of 23 statements) found similar biologic pathogenesis, and similar or better effectiveness and safety in children older than 2 years compared to adults. Pharmacokinetics were similar in adolescents but dissimilar in younger children. The review also found sufficiently accurate noninvasive endpoints to reflect post-induction treatment response. There was no significant added benefit for ileocolonoscopy over sigmoidoscopy in ulcerative colitis. Drugs should be approved in children >12 years and ≥40 kg based on extrapolation from adult and real-world data.

For affiliations refer to page 22.

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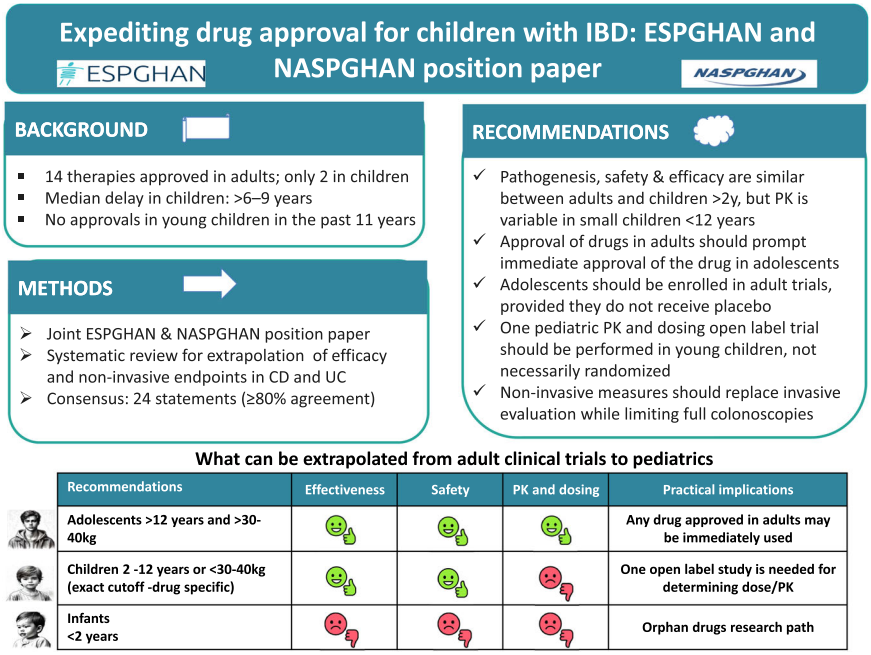
While efficacy may be extrapolated to children <40 kg, pharmacokinetics cannot and thus one open-label single-arm study should be performed to establish a dose that matches adult exposure-response from the adult trial in which adolescents may be enrolled if not exposed to placebo. Full colonoscopies should be minimized in the pediatric dosing trial. Efficacy in patients with infantile IBD cannot be extrapolated from adult data.



1 | INTRODUCTION

Advancements in inflammatory bowel disease (IBD) research have significantly increased the portfolio of efficacious medications for treating adults aged 18 years and older. Unfortunately, the benefits of these advances have been limited for children with IBD because of inordinate delays in pediatric drug approval. Of the 14 biologics and oral small molecules now approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for adults with IBD, only infliximab and adalimumab received pediatric approval, long after adult approval (8 and 6 years later for Crohn's disease [CD], and 6 and 9 years later for ulcerative colitis [UC], respectively [Table 1, Figure 1]). Two medications, etrasimod in UC and risankizumab in CD, have been approved for those ages 16 and above in a few countries based on a few adolescents included in the adult trials, and ustekinumab was recently approved by the EMA for children with CD weighing >40 kg. One in three children with IBD will be exposed to medications not approved in pediatrics.[1,2] Third-party payers commonly refuse to cover treatment for children without an approved pediatric IBD indication, depriving them of effective therapies. Even when authorized, off-label use occurs in the absence of large safety data registries and pharmacokinetic/pharmacodynamic (PK/PD)-based dosing studies, which are especially pertinent in children weighing <30–40 kg who often require different dosing strategies. A recent study from the Porto group of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) showed that adalimumab doses in 78 children younger than 6 years of age ranged from 20 to 200 mg/body surface area (BSA) cumulative induction doses, illustrating the broad heterogeneity in dosing regimens when specific studies have not been conducted.[3]

The urgency of moving forward with timely pediatric approval is underscored by the increased severity of disease on average, in children compared to adults.[4] This is in addition to the effects of inadequately treated chronic inflammation on growth,[5] the lifelong consequences of missing education and developmental milestones in a crucial period of life, and the long-term harms of active disease associated with delayed treatment. This urgency remains unaddressed by the pace of regulatory drug approval for children by both the FDA and the EMA.

It has been 11 years since the adult approval of vedolizumab and 9 years since the approval of ustekinumab, yet neither is currently approved for use in children (Table 1). Instead of taking the necessary steps to shorten this unacceptable delay, there are now extra hurdles for clinical trials such as three ileocolonoscopies over 1 year in both pediatric CD and UC, as suggested

What is Known

- Fourteen advanced therapies have been approved thus far for adults with inflammatory bowel diseases (IBD) but only two are approved for children; none in last 11 years.
- Regulatory agencies have accepted partial extrapolation from adults to children with IBD, leading to studies, underpowered to prove efficacy, yet still more than one controlled trial are required.
- Two drugs have been approved in some countries from the age of 16 years based on the inclusion of adolescents in adults' trials.

What is New

- This ESPGHAN-NASPGHAN position paper and systematic review supports extrapolating efficacy and safety from adults to children older than 2 years, and pharmacokinetics to children >12 years and ≥30–40 kg (exact weight cutoff may be drug-specific).
- Therefore, drugs should be approved in adolescents >12 years and >30–40 kg based on the adult trials while one open-label pharmacokinetic study with suboptimal dosing is required in younger children. Infants' approval cannot be extrapolated from adults.
- At most two ileocolonoscopies in Crohn's disease, and three sigmoidoscopies in ulcerative colitis can be done in a year, supplemented by noninvasive biomarkers.

by the FDA (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-inflammatory-bowel-disease-developing-drugs-treatment). According to accepted ethical principles, the repeated general anesthesia may be justified when the child directly benefits from the procedure, but three ileocolonoscopies deviates significantly from clinical practice in most patients,[6] especially in UC when mostly sigmoidoscopy is utilized, and thus may be ethically problematic.[7]

Since the adult approval of vedolizumab and ustekinumab, the manufacturers have reported PK/PD data in clinical trials,[8,9] and both medications have extensive retrospective and prospective pediatric real-world clinical and safety data[8–18]; yet these drugs still lack pediatric regulatory approval. These barriers continue even for more recently approved therapies (Boxes 1 and 2).

Pediatric drug development and drug approval processes face numerous challenges, including the smaller absolute number of pediatric patients with IBD compared to adults and multiple age-specific factors that complicate recruitment.[20–22] For example, children may be more sensitive to repeated blood tests and other invasive procedures and parents less tolerant of untreated active disease during screening periods prolonged due to long washout periods that do not match real-world practice. Nontreatment has recently been associated with harm in a meta-analysis of adult clinical trials.[23] As a major difference from adult trials, however, parents are obliged to make all decisions in the best interest of their children and cannot consent to be altruistic by permitting placebo in a condition that can be treated effectively. Consequently, as clinical trials deviate from standard practice, children and their caregivers are less likely to participate, unless deviation is clearly in their child's best interest. This reluctance is compounded when pediatric trials typically occur long after drug approval in adults, allowing some patients in many countries off-label access to the drug. Taken together, trial design for children must prioritize feasibility and address age-specific ethical considerations.

Over the last decade, the pediatric IBD community has tried to constructively engage with regulatory agencies and the pharmaceutical industry to adapt the regulatory process for the pediatric population. Multiple recommendations have been made for trial design in several initiatives,[24–29] with the aim to improve trial feasibility while maintaining the accrual of sufficient supporting data. Most importantly, these recommendations have emphasized the central data-driven stance of the scientific community and pharmaceutical industry that extrapolation from adult trials to children is justified and necessary in IBD, rather than conducting underpowered studies to confirm effectiveness previously demonstrated in large, well-designed adult trials.

Pediatric extrapolation is based on assessing relevant similarities in disease characteristics, drug pharmacology, and treatment response between the target pediatric population and adults or other reference pediatric populations. While, historically, extrapolating safety data was considered unacceptable, the recent International Council for Harmonization (ICH) E11A Guideline on pediatric extrapolation that has been endorsed in 2024 by the EMA (https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e11a-pediatric-extrapolation-step-5_en.pdf) and in 2025 by the FDA (https://www.federalregister.gov/documents/2024/12/30/2024-31026/e11a-pediatric-extrapolation-international-council-for-harmonisation-guidance-for-industry), has expanded the concept to include also safety considerations. The EMA ICH E11A Guideline determines the required framework for understanding the factors influencing disease, drug pharmacology, treatment response, and safety in both the pediatric and adult populations. The evidence provided in this ESPGHAN/NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition) position paper is based on the framework determined in the ICH E11A guideline.

TABLE 1 Comparison of FDA adult and pediatric IBD license approval.

Medication	Approval for adult IBD		Approval for pediatric IBD		Approval for other pediatric conditions
	CD	UC	CD	UC	
Infliximab	1998	2005	2006	2011	JIA 2010
Adalimumab	2007	2012	2014	2021	JIA 2008
Certolizumab	2008	–	/	/	JIA 2024
Golimumab	–	2013	/	/	JIA 2020
Vedolizumab	2014	2014	/	/	/
Ustekinumab	2016	2019	2025[a]		Juvenile psoriasis 2020, Juvenile PsA 2022
Risankizumab	2022	2024	/	/	Juvenile PsA 2022, JIA 2024
Guselkumab	–	2024	/	/	
Mirikizumab	2025	2023	/	/	
Tofacitinib	–	2018	/	/	JIA 2020
Upadacitinib	2023	2022	/	/	JIA 2024
Filgotinib		2021	/	/	/
Ozanimod	–	2021	/	/	/
Etrasimod	–	2023	/	/[b]	/

Note: "/" indicates no pediatric approval.

Abbreviations: CD, Crohn's disease; FDA, Food and Drug Administration; IBD, inflammatory bowel diseases; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; UC, ulcerative colitis.

[a]Approval in the European Union is only for patients weighing >40 kg.

[b]Approved in adolescents >16 years of age in the European Union, the United Kingdom, and Israel.

Regulators have previously accepted partial extrapolation,[30,31] allowing small-scale trials, which are always underpowered to prove statistical efficacy.[31–33] Moreover, placebo was removed from pediatric trials with the use of historical placebo rates from adult trials. More recently, drugs were approved in the United Kingdom and Israel for adolescents 16 years and older based on a small number of adolescents included in adult randomized controlled trials (RCTs) (12 in the risankizumab trial [NCT#03105102] and three in the etrasimod trial [NCT#03945188]). Unfortunately, the nine adolescents included in the upadacitinib adult trial (NCT#03006068) did not lead to approval in any country and the majority of countries still do not have approval down to 16 years of age for any drug.

The harmful delays in drug approval in children have triggered the current joint initiative of the ESPGHAN and NASPGHAN after initial smaller individual efforts.[34–36]

We have reviewed the conceptual similarities and differences in children and adults with IBD and pragmatic opportunities to optimize the feasibility of clinical trials in children, while stressing the urgent need to accept extrapolation from trials in adults. This position paper offers a path forward, accepted by the pediatric scientific community and patient representatives (Table 2).

2 | METHODS

The Pediatric IBD Porto and Interest Groups of ESPGHAN, along with the NASPGHAN IBD Committee, issued a call for participation in June 2024. Following the call, 19 international experts in pediatric IBD (10 from ESPGHAN and nine from NASPGHAN), including three early career members, were selected by the steering committee (D.T., A.A., J.A., and J.P.). Two representatives from patient organizations were included, one from the European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA) and the second from North America (The Pediatric IBD Foundation). Eight topics were defined a priori by the steering committee and assigned to specific working groups, including extrapolation of efficacy (as justified by comparable biologic pathogenesis, clinical responses to therapies, safety, and pharmacokinetics), study types required for registration, endpoints in pediatric drug registration trials in CD and UC, dosing considerations and perspectives of patients/caregivers. The sections were merged and reordered by iterative process of all authors to maximize flow and readability of the final manuscript, which included the following subheadings: biologic similarities between pediatric and adult IBD, pharmacokinetics, clinical response and safety of treatments in pediatric and adult IBD, noninvasive biomarkers in CD and noninvasive markers in UC. Other sections were formulated based on the input of the different sections, including proposed extrapolation plan, how to utilize endoscopic assessments in clinical trials and patients/caregivers' perspective as a separate box.

To identify clinical evidence supporting the extrapolation of efficacy and noninvasive endpoints for pediatric drug registration trials in CD and UC, systematic literature reviews were conducted by assigned working groups using the PICO (patient/population, intervention, comparison, and outcomes) model approach. Electronic searches were performed in July 2024 using Scopus, Medline, Embase, Web of Science, and Cochrane databases (Supporting Information S1: Appendix S1). Titles and abstracts were reviewed by two independent reviewers to exclude irrelevant studies, and full-text articles were assessed for eligibility. Discrepancies between reviewers were resolved by consensus. The PICO question for the

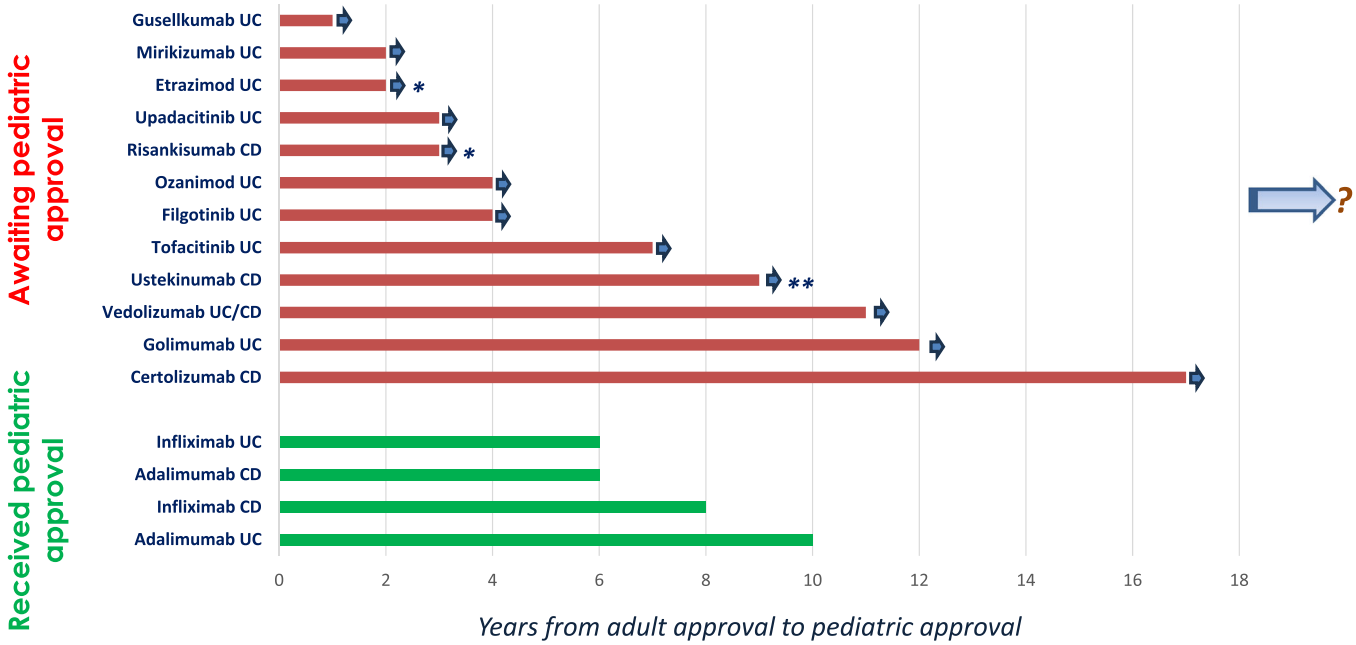


FIGURE 1 Time to first FDA/EMA approval of drugs in PIBD from the time of adult registration. *Approved in some countries in adolescents >16 years, ** approved by the EMA in adolescents >40 kg. CD, Crohn's disease; EMA, European Medicines Agency; FDA, Food and Drug Administration; PIBD, pediatric inflammatory bowel diseases; UC, ulcerative colitis.

noninvasive endpoints was formulated as: P—pediatric patients with CD/UC; I—evaluation by one of the identified Noninvasive measures of intestinal inflammation (Supporting Information S1: Appendix S1); C—evaluation by colonoscopy; and O—performance characteristics of noninvasive biomarkers in reflecting colonoscopic activity. Two sections that included broad range of topics and study designs were based on scoping and not systematic review and are labeled accordingly below. This flexible search with less rigid criteria allowed more informative sections.

Each working group was asked to generate specific statements/recommendations with supportive text and, when relevant, tables of evidence and preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow charts (Supporting Information S3: Tables S1–S11, Supporting Information S2: Figures S1–S3). The text and statements were iterated by email with the steering committee members until refined. The entire group then voted on all statements in three rounds, using a web-based voting platform enabling the insertion of specific comments. The statements were revised based on the comments received from the voting platform and from two virtual meetings. Only statements supported by at least 80% of the group advanced to each next round of voting, resulting in 24 endorsed statements. The statements and text were sent to all members of the Porto group, to members of some pharmaceutical companies and contacts in the EMA and FDA for review and comments, if received, were considered exclusively by the authors without voting or editing rights. The supporting text provides the evidence on which the statements were drafted, while summarizing the interpretation of the panel of the included manuscripts.

The final version of the text and statements was reviewed by all authors and approved by the sponsoring societies, ESPGHAN and NASPGHAN.

3 | SUMMARY STATEMENTS (22 VOTING AUTHORS)

3.1 | Extrapolation and study types

1. There is no evidence that differences in pathogenesis and pathobiology between pediatric and adult patients with IBD are associated with differences in response to pharmaceutical therapies, except for monogenic disease (agreement 21/22).
2. In general, efficacy and drug-related safety outcomes in children older than 2 years are comparable to adults (agreement 22/22).
3. Pharmacokinetics are consistently similar between adults and children ≥30–40 kg but in smaller children they may vary (exact weight cutoff may be drug-specific) (agreement 22/22).
4. Taken together, approval of drugs in adults should prompt immediate approval of the drug in adolescents weighing at least 30-40 kg, while the exact cutoff should be individualized by PK modeling (agreement 22/22).

BOX 1: Example of the problem

In the pediatric CD upadacitinib registration program, twice as many patients are needed compared with the pediatric juvenile idiopathic arthritis (JIA) and psoriatic arthritis (PsA) study, requiring 92 sites. This type of trial can take years to complete and indeed, the estimated study completion is 2034. The investigational plan for upadacitinib in pediatric CD (NCT#06332534) is as follows: "The study is conducted in two periods: Period 1 is comprised of two phases: a 12-week open-label induction phase which means that the study doctor and participants know that participants will receive UPA Dose-A (or the adult equivalent based on body weight) followed by a 52-week double-blind maintenance phase meaning that neither the participants nor the study doctors will know which dose of upadacitinib will be given (UPA Dose B or Dose C). Period 2 is a 156-week open-label extension of Period 1. Approximately 110 pediatric participants with moderate to severely active CD will be enrolled at approximately 92 sites worldwide." In contrast to this description, the same medication was approved in children for the treatment of JIA and PsA, and the process is described by the pharmaceutical company on June 4, 2024: "supported by evidence from well-controlled studies in adult patients with rheumatoid arthritis (RA) and PsA, pharmacodynamic data from adult patients with RA and PsA, as well as 51 pediatric patients with JIA with active polyarthritis, in addition to safety data from 83 pediatric patients with JIA and active polyarthritis. Upadacitinib plasma exposure in children with JIA and PsA at the recommended dosage are predicted to be comparable to those observed in adults with RA and PsA based on population pharmacokinetic modeling and simulation" (https://news.abbvie.com/2024-06-04-RINVOQ-R-upadacitinib-Now-Available-for-Pediatric-Patients-2-Years-and-Older-with-Polyarticular-Juvenile-Idiopathic-Arthritis-and-Psoriatic-Arthritis).[19] For comparison, since 2014, the FDA has approved three agents for pediatric psoriatic arthritis and five agents for pediatric psoriasis. The EMA has approved two agents for pediatric psoriatic arthritis and five agents for pediatric psoriasis. During this period, only a single agent was approved for pediatric UC, 9 years after adult approval.

BOX 2: Putting this into patient and parent perspective (written by parents of children with CD)

Imagine being the parent of a child with newly diagnosed IBD after 1–2 years of unexplained "belly aches" and fatigue. You're faced with treatment decisions involving powerful medications that suppress your child's developing immune system. Everything is new and there is so much to consider! You understand with concern that most treatment options are used by pediatric gastroenterologists "off-label" without available long-term efficacy or safety data. You face a fight with the insurance and worry if it will be approved. You are then approached to be included in a clinical trial and read with concern the long consent form and the extra procedures required. You wonder, why would I enroll my child in such a trial when possibly I could get the medication by petitioning for off-label use? The risk that your sick child will be untreated during a washout period, or with subtherapeutic dosing seems unacceptable when other effective treatment options are available. You want to protect your child from more suffering associated with additional procedures, but also concerned about off-label use. There is no easy solution, and you are left wondering why your child cannot have the same terms and opportunity as a similar CD patient older than 18 years. After decades of inaction by the regulators, children continue to suffer and parents and physicians continue to battle for off-label medication coverage.

5. Adolescents who are both ≥12 years of age and ≥40 kg in weight should be enrolled in adult trials if given active drug and not placebo to provide pediatric data for modeling and simulation of dosing in younger children (agreement 22/22).
6. Pharmacokinetics in children <30–40 kg may be modeled from a combination of adults, adolescents included in adult studies, and other pediatric indications but must be verified in one properly designed pharmacokinetics trial (agreement 22/22).
7. The pediatric pharmacokinetics trial should be open label and not necessarily randomized since the sample size in pediatrics will always be underpowered for determining effectiveness (agreement 21/22).
8. The exact sample size and weight cutoff of the pharmacokinetics trial (<30 or <40 kg) should be determined individually for the drug under study,

TABLE 2 Specific challenges for pediatric IBD trials.

Specific problem pediatric IBD trials	Solutions
Small patient population compared to adults	1. Accepting extrapolation of efficacy from adult trials, thus the pediatric trial does not need to be powered for efficacy superiority. 2. Pragmatic design to increase acceptance and recruitment.
Repeat blood tests add to patient anxiety and suffering	Align blood test with the standard of care as much as possible
Repeat endoscopy creates increased burden, anxiety, suffering, and risk, including anesthesia, bowel preparation in children	Replace some procedures with noninvasive measures while relying on extrapolation for efficacy from adults: 1. In CD limit ileocolonoscopies to at most twice within 1 year. Postinduction assessment should utilize noninvasive markers as intestinal US and the MINI index. 2. In UC, perform sigmoidoscopy rather than full colonoscopy and limit to 2–3 in 1 year. Postinduction assessment may be supplemented or replaced by noninvasive markers as PUCAI, TUMMY-UC, calprotectin and intestinal US.
Paucity of data in prepubertal children leads to inaccurate dosing recommendations.	Accepting extrapolation for efficacy from adults may lead to a more feasible and pragmatic study design, which will improve enrolment in the younger age group, thus allowing to validate the extrapolated dosing from adults.
Insufficient sample size in pediatric trials to describe uncommon adverse events and compare doses in the absence of placebo which is unethical in children.	1. The pediatric trial may by open label without comparing two interventions which are anyway underpowered to show differences. In any case, arms with subtherapeutic doses/ interventions should be avoided for ethical reasons. 2. In addition to the regulatory trial, it is necessary to perform early phase 4 large multicenter prospective cohort registries to record safety and supplement data for effectiveness and dosing.

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; MINI, mucosal inflammation noninvasive; PUCAI, Pediatric UC activity index; UC, ulcerative colitis.

based on modeling and simulations (agreement 22/22).

9. Optimal dosing should be used in all study arms in pediatric trials. Placebo, sham, or doses demonstrated to be subtherapeutic in prior studies should not be permitted. They are unethical in children, reduce feasibility of enrollment, and are not expected to be informative given the underpowered sample size of pediatric studies (agreement 22/22).
10. The design of the pediatric study establishing pharmacokinetics should be planned no later than the time of completion of the adult phase 2 trial, once dosing is established. The pediatric study should be initiated within 6 months of completion of the adult phase-3 trial to ensure registration of children shortly after the adults (agreement 22/22).
11. While safety profile can be reasonably predicted in children >2 years of age based on adult data, it must be confirmed in large long-term post-registration surveillance registries. These should be fully transparent, led and analyzed by pediatric IBD experts, with support from pharmaceutical companies (agreement 22/22).
12. Monogenic forms of IBD are rare, have different and diverse disease mechanisms, and should be considered orphan indications. They are particularly enriched among patients with infantile-onset IBD (i.e., <2 years of age). Patients with monogenic forms of IBD should be assessed in specialized trials, including compassionate use protocols, as well as using real-world data (agreement 22/22).

3.2 | Endoscopic assessment and noninvasive alternatives in CD

13. Ileocolonoscopic assessment is the gold standard for assessing mucosal healing (MH) and should be required at most twice in each study: that is, at baseline and study end (agreement 22/22).
14. Noninvasive objective measures, including serum and fecal biomarkers, magnetic resonance enterography (MRE), and/or intestinal ultrasound (IUS), should be used for assessing postinduction interim therapeutic response between the two ileocolonoscopies rather than requiring a third ileocolonoscopy (agreement 22/22).
15. The pediatric CD activity index (PCDAI), weighted PCDAI (wPCDAI), and their derivatives allow the determination of change in disease activity in response to therapy but are inadequate as sole biomarkers of MH (agreement 22/22).
16. Fecal calprotectin (FC) is correlated with endoscopic activity in CD, making it a useful

noninvasive biomarker for assessing postinduction response in clinical trials (agreement 22/22).
17. The mucosal inflammation noninvasive (MINI) index is superior to measuring calprotectin alone. The MINI index is highly associated with endoscopic healing (EH) making it a useful for noninvasive assessment postinduction response and may substitute for early postinduction ileocolonoscopy in pediatric clinical trials (agreement 22/22).
18. MRE is the preferred imaging modality in clinical trials using mult-item measures of inflammation, specifically the pediatric Crohn's MRE index (PICMI) which is validated for pediatrics and does not require rectal enema (in contrast to the adult MaRIA score) or intravenous gadolinium. MRE could be assessed as early as 3 months after induction for radiologic healing and radiologic response (agreement 22/22).
19. In children in whom MRE is not feasible (e.g., young children who require sedation), IUS may supplement the assessment of disease activity, as reflected by increased bowel wall thickness (BWT), hyperemia and loss of bowel wall stratification (BWS) (agreement 22/22).

3.3 | Endoscopic assessment and noninvasive alternatives in UC

20. Sigmoidoscopy is a sufficient tool for assessing endoscopic activity and treatment response in UC. Healing of the rectosigmoid reflects pancolitis healing with an accuracy of >90%. Therefore, complete colonoscopy offers little benefit over sigmoidoscopy during follow-up and should not be included as an outcome measure in clinical trials of pediatric UC (agreement 22/22).
21. Pediatric UC activity index (PUCAI) < 10 is recommended as the cutoff for approximating endoscopic remission with high accuracy. Therapeutic response is reflected by a change in the PUCAI score of at least 20 points (agreement 22/22).
22. FC levels are correlated with endoscopic activity in pediatric UC, making it a useful noninvasive biomarker for assessing postinduction response in clinical trials (agreement 22/22).
23. The TUMMY-UC is a patient- and observer-reported outcome (obsRO) measure for pediatric UC. It may serve as an additional noninvasive tool to reflect endoscopic remission (agreement 21/22).
24. IUS may be used to supplement assessment of bowel inflammation as early as 2 months following an intervention, with an accuracy of 80%–90%. The most common three criteria used to indicate inflammation are BWT, hyperemia, and loss of BWS (agreement 22/22).

4 | PART I

4.1 | Review of evidence exploring similarities and dissimilarities between pediatric and adult IBD

It has been widely accepted by the scientific community that the underlying pathophysiology, clinical expression, and response to therapy are generally closely aligned, although not identical in adult and pediatric IBD.[37] The aforementioned ICH E11A guideline stresses that rather than relying on rigid categories of extrapolation (e.g., full, partial, or none), it is essential to acknowledge that a continuum of similarity and dissimilarity in disease characteristics, drug pharmacology, and treatment response may exist between the populations. It is also recommended to highlight specific subgroups for which extrapolation may not be possible.

For establishing the extrapolation concept, all relevant data sources should be utilized, including clinical trials, real-world data, PK/PD studies, nonclinical mechanistic studies, and expert opinions. Accordingly, we reviewed the similarities of biological basis, therapeutic response, PK, safety, and clinical outcomes of pediatric versus adult IBD to support an extrapolation concept for children with IBD.

4.1.1 | The biologic similarities between pediatric and adult IBD and the implication for therapeutic response to treatment

The presumed pathogenesis of IBD is an aberrant immune response in genetically susceptible hosts in the presence of yet poorly understood environmental factors including components of the enteric microbiome. In general, despite some reported differences, as reviewed below, there is little evidence to indicate different pathogenic immune mechanisms in the pediatric and adult IBD populations. This section was based on a broad scoping review of literature and not systematic review.

4.1.2 | Genetics

Over 300 genetic loci have been identified so far in association with IBD, with only rare association signals suggesting additional enrichment in very early-onset disease.[38] Polygenic risk scores that sum the contribution of individual risk loci have found no significant difference (or minimal increase) in children with IBD compared to adults.[39,40] Most individual loci, as well as a sum score of hundreds of risk loci, suggest a similar genetic basis underlying IBD susceptibility between pediatric- and adult-onset patients with IBD. For

instance, the protective role of loss-of-function variants in interleukin (IL) 23 R found in children[41] and adults[42] with IBD is reflected by a similar response to therapies targeting IL-12/23p40 (ustekinumab) or IL23p19 in children and adults.[11,13,14,37,43] More relevant than pediatric or adult age of onset is the emerging recognition of shared and different IBD risk loci between ethnic populations. For instance, in different ethnic groups, there are different allele frequencies or effect size in susceptibility loci linked to genes *NOD2, TNFSF15, ATG16L1, IL23R, and IRGM*.[44] A study by Li et al. suggested fundamental similarities between pediatric and adult IBD populations, which the concept of extrapolation relies upon.[45] Up to 75% of genes differentially expressed in UC compared with healthy controls were the same in pediatric and adult patients, while <10% of genes were unique to pediatric or adult patients. Further, the expression of upstream regulators that control the differentially expressed genes (including tumor necrosis factor [TNF]-α) were almost 100% identical between the age groups.

An exception may be patients with infantile-onset IBD (i.e., <2 years of age), where little evidence is available and among whom the rare monogenic disorders associated with chronic bowel inflammation are most likely to occur. The over 100 monogenic forms of IBD identified to date,[46,47] are caused by genetic variants that affect key functions in the epithelial barrier and/or aspects of the innate and adaptive immune system, antimicrobial immunity, lymphocyte selection, and regulatory T cells. Consequently, treatments in this population could differ from those in later childhood and adulthood.[48,49] Monogenic disorders are exceptionally rare and may be found primarily in infants with disease onset before 1 year of age and less so in those with very early onset disease (2–5 years) or older children (estimated overall <0.5%).[50] Clinical trials typically exclude patients with monogenic IBD per protocol, and as identified in the literature review described herein.

4.1.3 | Epigenetics

Environmental exposure factors have a substantial impact on the epigenetic makeup in different developmental phases from birth to adulthood. The DNA methylation age at defined loci—the so-called "epigenetic clock" are epigenetic markers reflecting cellular DNA methylation.[51] Those markers reflect the epigenetic age compared to chronological age in different cell types and may reflect chronic inflammation which accelerates the biologic age. Differences in the IBD epigenome can be compared, therefore, between pediatric- and adult-onset IBD. Multiple studies have evaluated the epigenome in pediatric-onset,[52,53] adult-onset,[52–55] and all ages.[52,56] Most IBD studies have evaluated the role of DNA methylation on IBD susceptibility[52,55] or their potential role as biomarkers.[53,57] Pharmacologic agents that affect epigenetic processes include histone deacetylase inhibitors (HDACi), histone acetyltransferase inhibitors (HAT), and DNMT (DNA methyltransferase inhibitors, but these have no current evidence of therapeutic efficacy in IBD.[55,58] DNA methylation profiles have been used as a predictor for anti-TNF-α drug concentration.[54] Comparative studies of epigenetics in IBD across patient age groups are rare. Age-related DNA methylation changes in pediatric versus adult IBD were apparent in cohorts examining $CD8^+$ T-cell DNA methylation.[59] Application of an "epigenetic clock" algorithm[51] confirmed a significant correlation between the predicted age based on DNA methylation and chronological age but this is not associated with different IBD susceptibility, disease mechanisms, or response to therapy between the pediatric and adult IBD population[59]; suggesting that age-related epigenetic differences are not associated with differences in disease course or response to therapies.

4.1.4 | Microbiome

The gut microbiome takes shape during early life, starting with postnatal colonization, while subsequent development is impacted by multiple environmental factors.[60,61] Despite some differences in the microbiome found in several studies between pediatric- and adult-onset IBD, the extent and nature of these differences remain unclear. Perinatal and early life events (within the first 2–3 years) include antibiotic use, mode of delivery, breastfeeding, early nutrition, and other exposures that are linked to microbiome and immune development; these have been associated with the risk of immune-mediated conditions, including IBD.[62,63] However, this critical window ends long before the age in which IBD typically emerges.[64–66] Few studies have compared the pediatric and adult microbiome, with most differences observed <3 years of life.[67,68] Very few studies have investigated age effects in IBD, but the general compositional and functional profile appears to be similar between children and adults with IBD.[69,70] Furthermore, evidence that the microbiome profile is associated with response to therapy is lacking, except for response to enteral nutritional therapy with a possible beneficial role for butyrate-producing bacteria; however, these effects are not age-specific.[71–75]

4.1.5 | Immunology

The immune system is immature at birth, evolving during a lifetime of exposure to multiple foreign challenges through adulthood to the decline of old age.[76] Innate immunity is particularly vital in the neonate (for

instance, due to immature neutrophil function and immaturity of adaptive immunity). The adaptive immune system from infancy to adolescence differs from that of adults; innate-like T-cells are observed in the neonatal period and T-cells from older children (aged 5–16 years) still show decreased pro-inflammatory cytokine secretion compared to adults.[77] However, there is no evidence that differences in age-related development of the immune system, impact the degree of response to IBD medications.

4.1.6 | Pharmacokinetics, clinical response, and safety of treatments in pediatric and adult IBD

It is widely accepted that not only the underlying pathophysiology, but also response to therapy is broadly similar in adult and pediatric IBD. We included nine papers in a systematic review after screening 1,914 identified records (Supporting Information S3: Table S1, Supporting Information S2: Figure S1). We then supplemented the systematic review by a scoping search for all phase 3 trials reporting on biologics or small molecules in the adult population, and for each, we identified the highest-order corresponding pediatric study (phase 3 > phase 2 > phase 1 > real-world cohorts). Table 3 summarizes the clinical and endoscopic outcomes of these studies (involving 11 different biologics), whereas Supporting Information S3: Tables S10–S12 provide details of each. It should be noted that multiitem measures used and timing of assessment differed between adult and pediatric trials.

In short, despite some differences in clinical phenotypes with pediatric disease having more extensive disease,[113–115] higher rate of colectomy,[116–118] and higher rates of perianal disease,[119,120] the identified evidence suggests that pediatric and adult patients with IBD respond similarly to treatment (Table 3, Supporting Information S3: Tables S10 and S11). The tabulated studies show that pediatric efficacy rates are generally comparable to or exceed those of the adult populations for the available drug trials. Higher efficacy rates in pediatric IBD could be explained by the shorter disease duration at the time of enrolment, as is well recognized as a factor influencing treatment response in CD.

Of the nine studies included in the systematic review of extrapolation of results from adult studies (Supporting Information S3: Table S1), five were post hoc analyses of phase I–III trials finding minimal effect of age on the PK properties of biologics and comparable exposure-response estimates, two were methodological papers that simulated PK properties based on publicly available data, and two (one registry-based and the other prospective) compared the effectiveness of biologic treatment between children and adults with IBD. Both found no differences in the measured outcomes or drug sustainability across the age groups.[121,122] Three studies reported on pediatric populations while comparing efficacy and pharmacokinetics with previous adult phase 3 studies. All three included only a small sample of those younger than 10 years and no patients younger than six. The first compared the pediatric REACH trial with the adult ACCENT I trial of infliximab in CD and found that the distribution of infliximab per kg body weight decreased as the total patient weight increased, but the pharmacokinetic properties of infliximab in pediatric CD patients could be extrapolated from the adult CD population.[123] Another study compared the data of infliximab in UC from the pediatric T72 trial and the adult ACT 1 and 2 trials[124] and found similar infliximab concentrations and similar exposure-response. The third study compared golimumab PK data from the pediatric PURSUIT-PEDS-PK UC trial and the adult PURSUIT-SC trial, showing no effect of age on golimumab pharmacokinetics, and similar exposure-response rates when evaluating clinical response and MH.[125]

A post hoc analysis of 11 adult studies of four biologic agents including 6283 participants showed a similar response in the 546 who had pediatric-onset disease compared to those with the adult-onset disease, suggesting that drug response is similar in disease initiated during childhood or thereafter.[37] The remaining publications explored modeling to extrapolate adult-based data to pediatric IBD patients on ustekinumab[126] and infliximab.[127] The latter is a case study of infliximab in pediatric UC, showing that sample sizes can be significantly reduced if prior information from adult studies is included in the analysis, which is the basis of Bayesian methodology. Other studies found that higher mg/kg dosing of biologics is needed in younger children compared with adolescents and adults as demonstrated for adalimumab, infliximab, ustekinumab and etrolizumab.[124,126,128–132] The observation that weight-based dosing becomes nonlinear and, at times, unpredictable in young children with a body weight <30 kg is not unique to IBD or biologics. Weight-based dosing of steroids results in lower serum drug levels than BSA-based dosing and the difference increases proportionally below 30 kg of weight.[133]

These aforementioned studies compared efficacy and PK properties in pediatric and adult patients with IBD, but there is also the opportunity to extrapolate PK properties from pediatric patients with other immune-mediated inflammatory diseases. Although not included in the systematic review, we highlight several studies from non-IBD diseases of shared drugs. For instance, in psoriasis, ustekinumab's PK properties and exposure-response rates are comparable between adults and children over 5 years of age.[134] In another study, Chang et al. proposed a simplified dosing

TABLE 3 Clinical outcomes in adult and pediatric IBD patients treated with biologics and small molecules (study design and other details of these studies can be found in Supporting Information S3: Tables S10–S11).

				Induction			Maintenance		
Drug, ref.	IBD type	Population	Trial phase	Clinical response (%)[a]	Clinical remission (%)[a]	Study population (*n*)	Clinical response (%)[a]	Clinical remission (%)[a]	Study population (*n*)
IFX [78–80]	CD	Pediatric	3	88	59	112	64	56	112
		Adult	3	81	33	108	48	38	573
IFX [81,82]	UC	Pediatric	3	73	64	60	NA	38	60
		Adult	3	67	36	364	46	35	364
ADA [83–87]	CD	Pediatric	3	82	28	192	42 (IFX naïve 55)	37 (IFX naïve 45)	188
		Adult (IFX naïve)[b]	3	50	36	299	NA	42	87
		Adult (prior IFX)[b]	3	52	21	301	NA	35	81
ADA [88–90]	UC	Pediatric	3	83	60	93	68	45	74
		Adult	3	55	19	576	30	17	494
VEDO [8,91,92]	CD	Pediatric	2	50	64	45	NA	36	64
		Adult	3	31	15	1115	46	39	461
VEDO [8,92,93]	UC	Pediatric	2	57	30	44	NA	53	73
		Adult	3	47	17	895	NA	45	373
GOL [94–97]	UC	Pediatric	1	60	43	35	60	55	20
		Adult	3	55	18	1064	50	28	464
UST [16,98,99]	CD	Pediatric	1	48	22	44	NA	41	25
		Adult	3	44	26	1369	59	53	1,281
UST [100,101]	UC	Pediatric	RW	67	47	58	NA	64	58
		Adult	3	62	16	961	27	NA	783
TOFA [102,103]	UC	Pediatric	RW	30	16	101	NA	24	101
		Adult	3	58	18	1139	62	41	593
UPA [104,105]	UC	Pediatric	RW	84	62	100	NA	NA	NA
		Adult	3	74	30	1488	77	52	451
MIRI [106,107]	UC	Pediatric	2	69	39	11	No studies		NA
		Adult	3	64	24	1281	NA	50	544
OZA [108]	UC	Pediatric		No studies					NA
		Adult	3	58	18	824	60	37	457
RISA [109–111]	CD	Pediatric	Abstract	74	65	23	No studies		NA
		Adult	3	65	45	1549	67	55	542
FIL [112]	UC	Pediatric		No studies					-
		Adult	3	NA	19	1348	NA	37	664

Note: RWE outcomes include pediatric participants receiving both monotherapy and dual therapy.

Abbreviations: ADA, adalimumab; CD, Crohn's disease; FIL, filgotinib; GOL, golimumab; IFX, infliximab; MIRI, mirikizumab; NA, not assessed; OZA, ozanimod; RISA, risankizumab; RW, real-world evidence; TOFA, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VEDO, vedolizumab.

[a]Maximal effect reported across different dosage regimens. See Supplementary Material for dose specifications.

[b]Maintenance data were derived from the CHARM trial based on responders at Week 4 (omitting data on nonresponders) and, therefore, inflated compared to the pediatric results from the IMAgINE trial.

regimen that could optimize tofacitinib levels across weight groups in patients with juvenile idiopathic arthritis (JIA) aged 2–18 years.[135] These data could be extrapolated when planning pediatric IBD studies. In addition to extrapolating PK properties, safety profiles could also be extrapolated across different indications, recognizing that some dosing and intervals will vary across indications, and the safety signal associated with these may differ slightly. For instance, the rates of anti-TNF-α-associated lymphomas are similar across indications.[136] Ustekinumab is approved for JIA and psoriasis over the age of 6 years and tofacitinib is approved for JIA over the age of 2, so these would act as appropriate comparators to IBD patients treated with the same medications.[137]

Our systematic review identified studies using different modeling designs to extrapolate adult PK data to the pediatric population. Recent studies often use physiologically based PK modeling. This design incorporates compartmental volumes corresponding to organ and tissue volumes and their growth and maturation with age into the simulations. While these studies are promising, especially for the youngest children with immature organs, extensive knowledge of drug properties is required, and simple allometric scaling (simulations based on body weight or surface area) could still be the most exact method for extrapolating PK properties to children over 5 years of age.[138]

Since genetic variation in the neonatal Fc-receptor (FcRn) influences anti-TNF concentrations in patients with IBD,[139] it is possible that response to biologic therapy may vary in infantile IBD (i.e., those younger than 2 years of age), but this population is typically excluded from pediatric IBD trials, given the rarity of the disease in this age group and the potentially dissimilar disease.

No evidence for new safety signals was found in the pediatric registry trials, the real-world studies or in previously published summaries we reviewed.[140] In Supporting Information S3: Tables S10–S12, pediatric rates of adverse events and serious infections were generally comparable to those reported in adult studies of the same medications. These observations should not preclude the need for collecting safety data in children exposed to new therapies but rather support sufficient similarities to indicate that safety should not be a barrier in the approval process. Moreover, due to the smaller numbers of pediatric patients, the sample sizes in pediatric trials are always too small to identify uncommon adverse events. Safety, therefore, may be extrapolated from prior adult trials, from other approved pediatric indications, and from real-world data from pediatric IBD. Most importantly, postmarketing standardized safety registries should additionally be employed with sufficient sample size to identify rare events. This should be mandated by the regulatory agencies.

5 | PART-II

5.1 | Proposed extrapolation plan for approving drugs in pediatric IBD

Based on the presented data in this manuscript, we propose a detailed extrapolation plan for children with IBD and discuss its implementation of drug development plan and study design.

5.1.1 | Disease similarity in pediatric extrapolation

Historically, pediatric extrapolation relied on binary determinations of disease similarity (i.e., yes or no). However, current approaches recognize that the evaluation of disease similarity is more nuanced, as detailed in the aforementioned ICH E11A guideline. The goal is not to determine if the diseases in the two populations are identical but rather to assess the degree of similarities and/or dissimilarities. We reviewed the pathophysiology, outcomes, drug pharmacology, safety, and treatment response in pediatric IBD, concluding that apart from infantile IBD (i.e., <2 years of age), pediatric IBD is sufficiently similar to adult IBD to base a new pediatric extrapolation plan, outlined in Figures 2 and 3 and below. The regulatory agencies should determine a framework that ensures pharmaceutical companies initiate the pediatric investigational plan as early as allowed and, in general, facilitates pediatric approval of all age groups.

5.1.2 | Adolescents

The similarity in the evaluated disease and drug characteristics is very high for adolescents who are >30–40 kg (corresponding to approximately ≥12–14 years) in all disease- and treatment-related aspects. As such, the proposed plan indicates that drugs approved in adults should automatically also be approved for use in children who are at least 12 years of age *and* weighing ≥30–40 kg (both criteria should apply); the exact weight cut-off determined by modeling and simulation of PK from the adults' clinical trial (see below). Nonetheless, including adolescents with diverse body weights in adult trials could provide initial pediatric data. It should be emphasized that the absence of adolescents in adult trials should not hinder drug licensing for this group after adult approval. Adolescent data primarily assist in designing trials for younger age groups and provide preliminary pediatric data but should not be mandatory. Pharmaceutical companies should utilize modeling and simulations based on adult and adolescent data to inform the extrapolation of dose proposals for validation in a small open label trial in the younger populations (as detailed below).

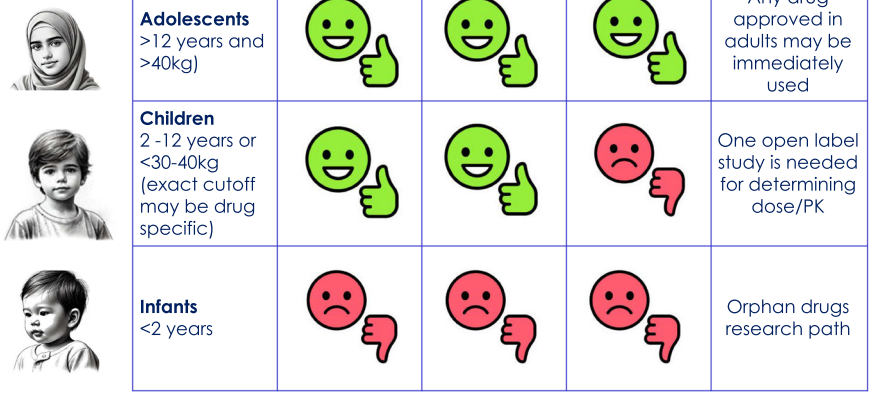


FIGURE 2 What can be extrapolated from adult clinical trials to pediatrics. The exact weight cutoffs should be determined individually for each drug based on modeling and simulations on data from adults and adolescents enrolled in prior trials, as well as from other pediatric indications and real-world data. PK, pharmacokinetics.

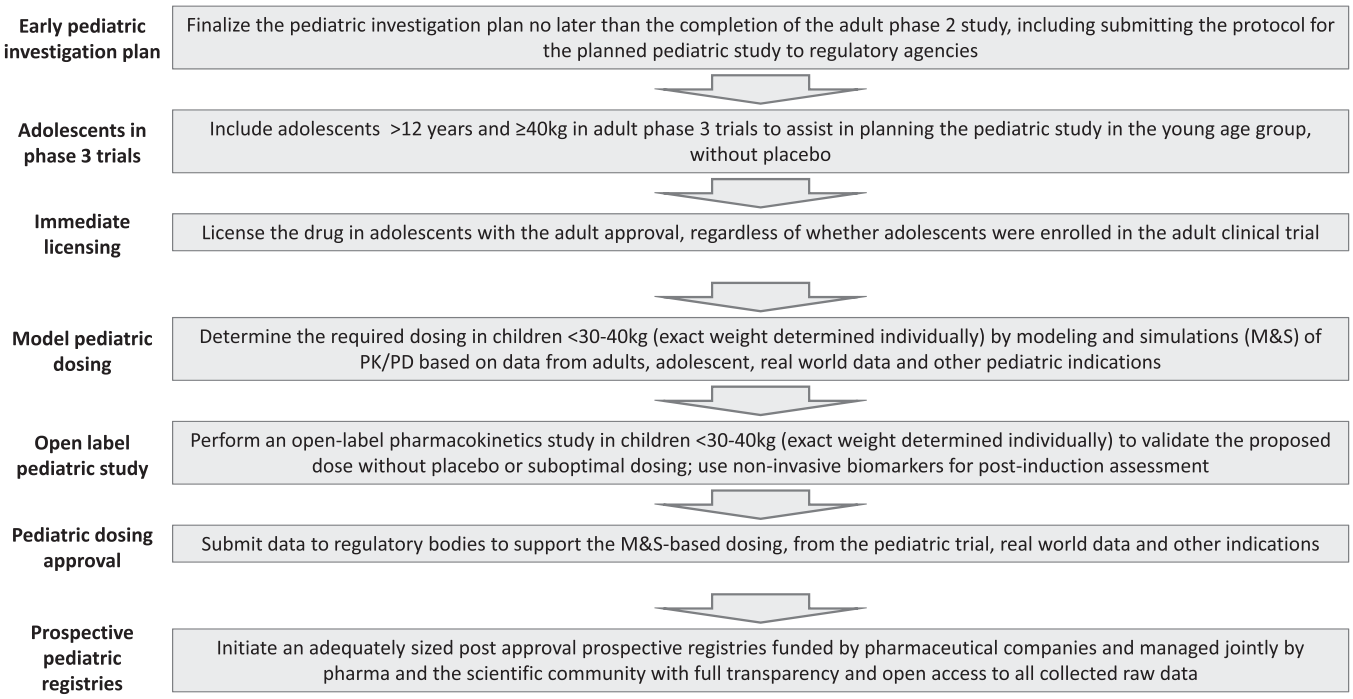


FIGURE 3 Proposed extrapolation path of pediatric approval of drugs in IBD. The reason for including adolescents in adult trials is to assist in the modeling and simulation for planning the pediatric trial in the youngest age group. It is not required for licensing the drug in adolescents which should be extrapulated from the adult data; The exact weight cutoffs should be determined individually for each drug based on modeling and simulations on data from adults and adolescents enrolled in prior trials, as well as from other pediatric indications and real-world data. IBD, inflammatory bowel diseases; PD, pharmacodynamic; PK, pharmacokinetics.

Quantifying relationships (e.g., dose-exposure, exposure-response) across weights forms the basis for simulations supporting dose selection in children <30–40 kg, which may include some children older than 12 years. Given the similarity in pathogenesis, the established wide therapeutic range in known IBD drugs and treatment response in IBD, adolescents and adults can be combined into a single efficacy analysis, yet the adolescence group must not be exposed to placebo.[21,26,27]

5.1.3 | Younger children (i.e., <30–40 kg or <12 years of age) who are older than 2 years

Based on the evidence presented in this position paper, efficacy may be extrapolated to children older than 2 years of age from adequately powered controlled trials in adults. However, while exposure-response in adolescents is similar to adults, younger children require different dosing considerations than adults to

reach similar exposure, as found in our literature review.

Pharmacokinetics in young children may be simulated by modeling from other populations (adults, adolescents included in adult trial and other pediatric populations) but the proposed dose should be validated in children weighing <30–40 kg in both UC and CD with sufficient sample size. To account for the subpopulation of children <12 years of age and >30–40 kg, inclusion of a representative proportion may be based on modeling from overweight/obese body composition in adults/adolescents. Pharmaceutical companies must be required to perform the pediatric study under a timeline that results in pediatric approval no greater than ~6 months from the date of adult approval. That requires planning the pediatric trial no later than upon completion of the phase 2 adult trial and possibly earlier. Since the main aim of the pediatric trial is to validate the pharmacokinetic dose-exposure relationship in prepubertal children, it could be uncontrolled and open-label. The exact sample size and weight cutoffs should be determined individually for each drug based on modeling and simulations on data from adults and adolescents enrolled in prior trials as well as from other pediatric indications and real-world data. For instance, adult dosing is recommended in those >40 kg for adalimumab[83] but in >30 kg for vedolizumab.[8] The analysis of the pediatric trial should assess whether the prespecified target exposure range observed in adults, adolescents, and other pediatric populations was achieved. An adaptive design allows for amendment of dosing after several children have been enrolled in each weight category, based on interim analyses without compromising the study's integrity or validity.

The proposed sample size must be sufficiently large to ensure adequate representation of children weighing <30 kg. Therefore, and since the trial is not powered to prove efficacy (extrapolated from adult data), invasive procedures and other requirements that may reduce recruitment feasibility should be limited. In a systematic review of noninvasive endpoints in pediatric CD and UC outlined below, we show that several biomarkers and indices reach sufficient accuracy to replace postinduction endoscopic assessments, especially full ileocolonoscopy. Once the full endoscopic effect of the drug has been reached, typically >6–9 months after treatment, one endoscopic assessment (sigmoidoscopy in UC and ileocolonoscopy in CD) can benchmark the efficacy results from adults.

The pediatric trial could provide some safety data but will be too small for meaningful conclusions. This should not be a barrier to pediatric approval as our review found very high similarity regarding safety between adults and children 2 years of age and older, without a concrete example of a distinct safety signal in children. Therefore, safety may be extrapolated from adult and adolescent data while full safety data can only be collected using large postapproval, real-world registries. These should be co-directed by pharmaceutical companies, pediatric IBD experts, and regulatory agencies. Regulatory agencies should request such postauthorization safety studies from companies. For instance, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) was established in 2017 by the rheumatology community to collect real-world data to augment efforts to improve patient outcomes. The Pediatric Rheumatology INternational Trials Organization (PRINTO) is a not-for-profit, nongovernmental, international research effort that has been operating for over 20 years and coordinates the development and standardization of international clinical trials for pediatric rheumatologic disease. Both organizations can serve as models for IBD trials.

5.1.4 | Infantile IBD (<2 years of age)

The only subset of pediatric IBD where efficacy may not be extrapolated from adults based on dissimilarities in pathogenesis and pathobiology, is those with monogenic disease, which most frequently occurs during infancy. As detailed previously, patients with monogenic forms of IBD are more likely to have different pathogenic mechanisms compared to pediatric and adult-onset IBD and require gene-specific or immune-pathway-specific therapeutic considerations.[49] Cases of IBD in infants are exceedingly rare, comprising <0.4% of all patients with IBD[141] and are typically excluded from pediatric trials. This leads to the exclusion of the vast majority of children with monogenic phenocopies of complex IBD even when the genetic diagnosis is unknown.

5.1.5 | The use of real-world data, prospective cohorts, and registries

Prospective and retrospective real-world data and registries should be leveraged for regulatory decisions, expedite drug development in pediatric IBD and to explore for rare safety and effectiveness outcomes postauthorization. Currently, medications approved in adults are being almost immediately used off label in children, providing a unique opportunity to collect data in support of the pediatric investigation plan. Examples are the prospective VedoKids study[18] and the retrospective Porto group initiative for ustekinumab.[11] These study types may provide further effectiveness and safety data, optimize dosing or serve as dynamic borrowing for underpowered studies.

Beyond cohort studies, longitudinal observational registries may provide pre and postregistration data with large sample size to explore rare outcomes, safety signals, and various treatment strategies (e.g., combination

treatment, early vs. late treatment, sequencing of the drug etc.). Current examples of such ongoing registries in pediatric IBD which include thousands of treated patients include the North American ImproveCareNow, The Canadian Children Inflammatory Bowel Disease Network (CIDsCaNN) and the European Paediatric IBD Network for Safety, Efficacy, Treatment, and Quality Improvement of Care (PIBD-SETQuality) inception cohort. The registries include also patients not typically represented in regulatory RCTs such as very young children,[142] those with mild or very severe disease or with comorbidity. These examples should support the drug approval path as articulated above.

A second type of registries are those focusing on safety and typically collected after the drug has been approved. These registries may be drug specific (e.g., the database for evaluation of pharmacovigilance in pediatric IBD to observe the long-term prognosis [DEVELOP] registry of infliximab and the Crohn's disease adalimumab postauthorization safety surveillance [CAPE] registry of adalimumab) or disease-specific (e.g., PIBD-SETQuality).[143]

Real-world evidence should be leveraged for regulatory decisions to expedite drug approval in pediatric IBD. Future work should increase the use of existing registries and real-world evidence to supplement trial data. There is an opportunity to facilitate the role of external control arms and observational data in supporting approvals for younger children.

6 | PART-III

6.1 | Noninvasive endpoints to reflect endoscopic inflammation

Once the regulatory agencies agreed to perform studies underpowered for superiority[31,32] and to remove the need for a placebo control arm following a wide scientific consensus,[21,26,27] then de facto efficacy evidence relies on adult trial data; this impacts on the choice of outcome measures in pediatric trials. The recent new requirement from the regulatory bodies for three full ileocolonoscopies within a year (baseline, postinduction at ~12 weeks, and end-of-study at 52 weeks) in pediatric IBD clinical trials raised serious feasibility and ethical issues. While endoscopic assessment remains the gold standard for the determination of MH, it does not diminish the need for utilizing noninvasive endpoints to limit the number of the invasive examinations. It enhances the likelihood of enrollment and is particularly applicable to UC where evidence suggests that flexible sigmoidoscopy can substitute for a full ileocolonoscopy. We performed a systematic review of the evidence to explore noninvasive measures that may reflect postinduction treatment response in CD and UC separately.

6.1.1 | UC

The systematic review of this section yielded 1462 manuscripts (565 for calprotectin, 417 for the pediatric UC activity index [PUCAI], 310 for IUS, 159 for sigmoidoscopy, and 11 for TUMMY-UC; Supporting Information S2: Figure S2). A summary of all pediatric studies identified in the systematic review may be found in Supporting Information S3: Tables S2–S5.

6.1.2 | PUCAI

Of the 417 manuscripts screened, 13 met the eligibility criteria and are included herein (Supporting Information S3: Table S2, Supporting Information S2: Figure S2). The PUCAI score has shown very strong correlations with endoscopic activity assessed by the Mayo endoscopic score (MES, $r = 0.75–0.95$),[144–147] the Rachmilewitz index ($r = 0.65$),[148] and the UC endoscopic index of severity (UCEIS, $r = 0.75$).[145] PUCAI also correlated well with histologic activity, as determined by the Nancy Histopathology Index ($r = 0.60–0.81$)[145,149] and the Robarts Histopathology Index ($r = 0.83$).[145] PUCAI-defined remission (i.e., <10 points) demonstrated a sensitivity of 72% and specificity of 98% for detecting pan-colonic EH.[145] In another study, all patients with PUCAI > 65 (i.e., severe disease activity) had Mayo scores ≥2, but 20% of patients with rectal MES of 1 or 2 had PUCAI < 10.[147] These findings should be interpreted cautiously, considering the retrospective nature of the study, the long interval between the assessments (i.e., 35 days), and endoscopic assessments based on photographs, potentially affecting the accuracy of mild disease. PUCAI is less accurate in the presence of primary sclerosing cholangitis (PSC),[150] although these patients are often excluded from clinical trials.

Several studies have evaluated PUCAI in the context of treatment response. In a post hoc analysis of 51 children treated with infliximab, PUCAI at Week 8 showed a strong correlation with the Mayo score ($r = 0.88$; $p < 0.001$). PUCAI < 15 reflected Mayo-defined remission with a sensitivity of 90%, specificity of 81%, and area under the receiver operating characteristic (ROC) curve of 0.93 (95% confidence interval [CI]: 0.86–1.0). A change in PUCAI of >20 points reflected Mayo-defined response with a sensitivity of 97%, specificity of 90%, and area under the ROC curve of 0.97 (95% CI: 0.92–1.0).

In an RCT of 60 children treated with infliximab, at Week 8 postinduction, Mayo score remission was achieved in 40% of patients, while clinical remission based on PUCAI was achieved in 33%.[81] While this is an indirect comparison it does reflect the general correlation between PUCAI and endoscopic activity. A similar trend was observed in a prospective cohort of 35 children treated with golimumab, where 43%

achieved Mayo clinical remission and 34% achieved PUCAI-defined remission at Week 6.[151] Conversely, a prospective study of 26 children treated with azathioprine found no correlation between PUCAI and Mayo scores at Weeks 0 and 52.[152] In another prospective study of 42 children with moderate to severe UC starting biologic or small molecules, a >55% decrease in PUCAI at Week 8 had the highest accuracy for detecting endoscopic response (area under the ROC curve [AUC] 0.83 [95% CI: 0.66–0.99]).[144]

PUCAI has also been explored as a predictive tool in some studies. A post hoc analysis of 51 children treated with infliximab showed that PUCAI at Week 8 predicted 1-year sustained steroid-free remission (SSFR) as effectively as EH, with AUC of 0.68 (95% CI: 0.5–0.87) for PUCAI and 0.66 (95% CI: 0.46–0.85) for EH.[153] In a multivariable logistic regression that included PUCAI score, endoscopic subscore, and C-reactive protein (CRP) at Week 8, PUCAI was the only significant predictor of 1-year SSFR. In a prospective study at diagnosis, median PUCAI scores were significantly lower in 78 patients with proctitis (25, interquartile range [IQR] 10–80]) compared to 796 children with extensive UC (40, IQR 10–85], $p \leq 0.001$).[154]

In a prospective study of 48 children, incorporating sigmoidoscopy as an additional item to the PUCAI did not add significant accuracy to the overall PUCAI performance, likely due to the very high correlation between the PUCAI and the Mayo score (0.95). This suggests that PUCAI reflects disease activity well even without sigmoidoscopy.[146] Incorporating albumin and CRP into the PUCAI yielded a weaker correlation with the Mayo score than the PUCAI alone.

Although evidence supports using the PUCAI to reflect EH or inflammation in children with UC, it is recommended that the Mayo score will be also completed for benchmarking the results of the pediatric study with those of the corresponding adult trial.

6.1.3 | TUMMY-UC

Of the 11 manuscripts screened, one met the eligibility criteria and is included herein (Supporting Information S3: Table S2, Supporting Information S2: Figure S2). The TUMMY-UC, a pediatric IBD-specific patient-reported outcome (PRO) measure, has been developed in a multicenter international study for children with UC and has two versions.[155] One is a PRO for children aged 8–18 years and the other is an obsRO measure for caregivers of children aged 2-7 years. In the latter, behaviors associated with subjective concepts are scored rather than the concepts directly (e.g., caregivers are asked to score behaviors associated with pain rather than scoring the degree of pain). A separate study determined the conceptual equivalence to provide a scientific basis for integrating the scores of the obsRO completed by the caregivers and PRO when used in studies that include both adolescents and young children.[156]

In the validation stage, the TUMMY-UC showed a moderate-strong correlation with all constructs of disease activity including IMPACT QOL questionnaire, calprotectin, PUCAI, and biochemical markers.[157] Importantly, TUMMY-UC < 9 points differentiated EH from active inflammation with a sensitivity of 93% and specificity of 84% (area under the ROC curve 0.85 [95% CI: 0.74–0.96]). Moderate disease, defined as 41–60 points, had a sensitivity of 94% and specificity of 94%. Responsiveness to change was high (AUC = 0.93, 95% CI: 0.86–0.99) and intra-rater reliability was excellent over subsequent days and after 10 days.

6.1.4 | IUS

Of the 310 manuscripts screened, 14 met the eligibility criteria and are included herein (Supporting Information S3: Table S3, Supporting Information S2: Figure S2). High-resolution examination of the bowel wall with IUS is a noninvasive, radiation-free means of assessing colonic inflammation and is well accepted by patients. Overall positive predictive value (PPV) of any abnormality on IUS in reflecting endoscopic remission from colitis was 77%–100% and the negative predictive value (NPV) 79%–92% (depending on the location of the involved segment).[158–160] Sensitivity 75%–100% (depending on the study and colonic segment, with higher sensitivity in the left colon) with specificity 91%–100%.[144,158–162] Two outlying retrospective studies, one from an older era of ultrasound machines with lower resolutions, showed lower association with endoscopic inflammation.[163,164]

In a retrospective study of 30 children with UC, the interobserver agreement for IUS with colonoscopic scoring of inflammation was excellent (interclass correlation coefficient [ICC] 0.93; $p < 0.001$).[162] Additionally, IUS categories of remission, mild, moderate, and severe disease had a very high concordance and agreement with endoscopic-based categorization (kappa = 0.94 [95% CI: 0.88–1]).[158]

BWT of ≥3 mm is considered significantly abnormal in most studies.[162,164] The mean/median BWT was 1.4–2 mm in the normal colon, 2.1–3 mm in mild, 3.3–4.5 mm in moderate, and 5.5 mm in severe disease.[158,165] In a retrospective study of 19 children with UC, the odds ratio (OR) for detecting inflammation was 3.8 for BWT 4–6 mm and OR of 6.0 for BWT 7–8 mm.[161] In another prospective study of 52 children, a BWT cut-off of ≥2.5 mm had sensitivity 66% and specificity 94% for moderate endoscopic inflammation

and a cut-off of ≥3.5 mm had sensitivity 92% and specificity 86% for severe inflammation.[166] A study exploring an ultrasound score which included the sum of BWT in the four colonic segments showed sensitivity, specificity, PPV and NPV of 81%, 90%, 77%, 92%, respectively.[160]

A prospective study of 50 children with UC showed that severity of endoscopic inflammation was independently explained in a multivariable model by BWT, increased vascularity, loss of the normal stratification of the bowel wall, and absence of haustra coli, forming the Civitelli UC Index (CUCI).[158] Another study affirmed that the combination of IUS parameters highly associated with EH: BWT > 3 mm, increased vascularity, loss of haustra coli, loss of BWS, and enlarged lymph nodes.[159] The Simple Pediatric Activity Ultrasound Score (SPAUSS) included increased BWT, mesenteric inflammatory fat, and increased vascularity.[161]

Among 52 children with UC, BWT, UC IUS score (UC-IUS), and Milan criteria (which includes BWT and hyperemia, had the highest correlation with endoscopic score (rho = 0.52–0.55) and differentiated endoscopic activity from healing (Mayo 1–3 vs. 0) with high AUC (0.89–0.93); SPAUSS, and CUCI performed less well.[166] Similarly, early changes in BWT had superior accuracy over IBUS-SAS and CUCI in reflecting endoscopic response after starting biologics in pediatric UC; BWT < 2.2 mm detected endoscopic remission (Mayo 0) with an AUC of 0.91, 95% sensitivity and 91% specificity and a BWT < 2.8 mm detected endoscopic improvement (Mayo 0–1) with an AUC of 1.0.[144]

The accuracy of IUS does not appear to be age-dependent.[163] IUS can identify rectal lesions only in one-third to half of children,[158,165] but otherwise has a 90% concordance[158] and 70%–100% sensitivity and specificity[159] with colonoscopy for disease extent. Perfusion measured by US has been also been associated with histological features.[167]

Showing the superiority of combining noninvasive measures, a prospective study of 32 children with UC found that combining IUS with colonic capsule endoscopy and FC achieved 95% sensitivity and 100% specificity, with PPV of 100% and NPV of 92% to differentiate EH from inflamed colon.[159]

6.1.5 | Sigmoidoscopy versus full colonoscopy

Of the 159 manuscripts screened, five met the eligibility criteria and are included herein (Supporting Information S3: Table S4, Supporting Information S2: Figure S1). Sigmoidoscopy is less invasive than a full colonoscopy, may be performed with lighter sedation and, therefore, safer. Moreover, it requires easier preparation (enemas only and a short fasting period). Several studies have examined the use of sigmoidoscopy compared to full colonoscopy in pediatric UC.

Studies in adult UC were not included in the systematic review but were searched independently to benchmark the pediatric literature. These demonstrated a strong correlation between sigmoidoscopy and pan-colonic activity.[168–170] For instance, in a prospective study of 100 patients with UC, sigmoidoscopy findings had an accuracy of 97% in detecting endoscopic activity throughout the colon, when a MES > 1 was used as the criterion (AUC of 0.98, sensitivity 95%, NPV 90%, specificity 100% and PPV 100%).[168] Moreover, biopsies from the sigmoid had an accuracy 98% in detecting histologic activity throughout the colon, with an AUC of 0.99, sensitivity of 97%, specificity of 100%, PPV of 100%, and NPV of 77%.[168] In another study of 124 patients with UC treated with etrolizumab, evaluating the videos of the full colonoscopy performed postinduction versus only the rectosigmoid segment showed a strong correlation for detecting EH, defined as a Mayo clinical score of 0 ($\kappa = 0.95$; $r = 0.95$; $p < 0.0001$).[169]

Pediatric studies showed similar high concordance between EH in sigmoidoscopy and the entire colon. A prospective cross-sectional study of 60 children showed that rectosigmoid UCEIS and MES scores were highly accurate in predicting EH throughout the colon (AUC: 0.99, 95% CI: 0.98–1.0) with sensitivity 100% and specificity 98%.[145] A rectosigmoid UCEIS score of 2 and a rectosigmoid MES score of 1 detected histological healing throughout the colon with high sensitivity (96% and 98%, respectively) and specificity (83% and 88%, respectively). Moreover, assessing the entire colon endoscopically did not improve the accuracy of histologic healing. Two retrospective studies, published as abstracts, demonstrated high association between left and right-sided endoscopic activity in children with UC. The first, with 57 children, showed that left-sided colonic healing predicted pan-colonic EH with AUC 0.98.[171] The second reported on 30 children who achieved complete EH (Mayo score 0) in the rectosigmoid, of whom only two (6%) had inflammation in the right colon, both mild (i.e., Mayo score 1); one of these patients had known atypical UC with rectal sparing at the time of diagnosis.[172] A third retrospective cohort of 58 children with UC showed that sigmoid MH predicted pancolonic healing with a specificity 83%, PPV 72%, and sensitivity and NPV of 100%.[173] Combining the sigmoidoscopic results with calprotectin<250 µg/g, improved the diagnostic accuracy for pancolonic healing with PPV 93%, NPV 91%, sensitivity 78%, and specificity 98%.[173] Finally, a prospective inception cohort of 85 children with UC showed that in 96.5% of children, the EH in the rectosigmoid region reflected EH in the entire colon.[174] When inflammation was present in the rectosigmoid, in 86% the degree of colitis reflected the maximal endoscopic severity of the entire colon. Taken together, these

findings suggest that sigmoidoscopy is a suitable routine posttreatment surveillance tool for pediatric UC patients to maximize feasibility and ethical considerations of clinical trials.

6.1.6 | FC

Of the 565 screened manuscripts, 12 met the eligibility criteria and are included herein (Supporting Information S3: Table S5, Supporting Information S2: Figure S1) with sample sizes ranging from 13 to 107 children. The reported FC cutoff levels for detecting EH in UC ranged from 39 µg/g (with a sensitivity 90% and specificity of 93%)[175] to 161 µg/g (sensitivity 90% and specificity 86%).[176] When evaluating FC's ability to detect histological activity in UC, cut-off values ranged from 87 µg/g (sensitivity 93%, specificity 92%)[177] to 275 µg/g (100% sensitivity, 72% specificity).[178] The latter cut-off is probably too high as it did not balance the very high sensitivity with the low specificity. A diagnostic accuracy meta-analysis of 25 adult studies, including 298 controls and 2822 patients with IBD, found that the optimal FC cutoff level for identifying EH from active disease was <100 µg/g with a balanced specificity of 78% and sensitivity of 80%; a cutoff <50 µg/g had higher sensitivity of 91%, but at a cost of low specificity of 61%.[179]

Overall, these studies reported a concordance between FC and endoscopic findings ranging from very good to excellent, confirming that FC can effectively detect inflammatory activity at both the mucosal and histological levels. Furthermore, FC demonstrated greater accuracy in identifying active inflammation than clinical symptoms and other inflammatory markers (e.g., CRP, erythrocyte sedimentation rate [ESR]).[180] Although there are significant differences between the cut-offs and reference standards used in studies, making it difficult to identify a clear FC cut-off for distinguishing patients with endoscopic inflammation from those with MH, a cut-off of <150 µg/g in identifying remission appears to be the most accurate.

Combining FC with clinical activity and noninvasive investigations, such as bowel US and video capsule endoscopy, increases the accuracy in identifying patients with active disease without the need for frequent endoscopic investigations,[159] which should be reserved only for patients in whom FC, along with other methods, suggest persistent inflammation. Moreover, the combination of FC with sigmoidoscopy may be highly accurate in reflecting pancolonic EH in patients with FC under ~150 µg/g.[173]

6.2 | CD

In total, 992 manuscripts were screened in the systematic review of CD (30 PCDAI, 20 MINI, 253 calprotectin, 428 intestinal US, and 261 MRE; Supporting Information S2: Figure S3).

6.2.1 | PCDAI

Of the 30 screened manuscripts, seven met the eligibility criteria and are included herein (Supporting Information S3: Table S5, Supporting Information S2: Figure S3). PCDAI was developed over three decades ago as a tool to assess disease activity in children with CD.[181] The original 11-item measure, which includes symptoms, physical examination findings, height velocity, weight gain, and laboratory parameters (hematocrit, albumin, ESR), was created based on physician global assessment of disease activity as the gold standard rather than endoscopic assessment of inflammation and was weighted judgmentally.[181] Over time, several abbreviated versions have been developed: wPCDAI, abbreviated PCDAI (abbrPCDAI), and short PCDAI (shPCDAI).[182–184] In comparison to the original PCDAI, wPCDAI has better feasibility, is more responsive to short-term change with at least similar validity,[183,184] and thus generally preferred for use in clinical trials. PCDAI cannot be used as a measure of MH, and as summarized in Table 1, correlations of PCDAI and wPCDAI with ileocolonoscopic assessment of MH range from fair to moderate (0.32–0.59).[184–190]

6.2.2 | MINI index

Of the 20 manuscripts screened, four met the eligibility criteria and are included herein (Supporting Information S3: Table S6, Supporting Information S2: Figure S3). Unlike the PCDAI, which was developed and validated using only physician global assessment of disease activity as the gold standard,[181] the mucosal inflammation noninvasive (MINI) index used endoscopy (SES-CD) as the gold standard, aiming to combine and mathematically weighted symptoms, serologic, and fecal inflammatory markers to better reflect mucosal inflammation.[190] The MINI derivation utilized 154 children with ileal/ileocolonic/colonic CD enrolled in the prospective, multicenter international ImageKids study[191] who had undergone ileocolonoscopy and provided a stool for FC determination.[191] Endoscopic disease activity was prospectively captured using the SES-CD with MH defined as SES-CD < 3. The MINI was validated using data from 168 children enrolled in three independent prospective cohorts.[190] The MINI index incorporates stool frequency and character with calprotectin, ESR, and CRP in a weighted, categorized index designed to identify children with EH.[190] The index assigns high weights on FC but the combination with CRP/ESR and clinical symptoms was significantly superior to FC alone. In the validation cohorts, 90%

with MINI ≥ 8 (93 of 103) had mucosal inflammation, including 59 (63%) with moderate–severe inflammation. Fourteen (22%) of the 65 patients with MINI < 8 did not have MH, but 95% of these had at most mild inflammation (i.e., the likelihood for moderate or severe inflammation with MINI index <8 is 5%).[190] A lower threshold of MINI < 6 increased PPV to 86%; based on SES-CD scores in 48 of 56 with MINI < 6 who had MH; endoscopic inflammation was mild in 7 and moderate-to-severe in only one.[190] The accuracy of MINI < 8 to detect MH varied slightly between disease location categories of the Paris classification. Sensitivity and specificity were slightly lower in ileal CD (L1), than in colonic and ileocolonic CD (L2/L3) on the combined data (L1: $n = 77$, sensitivity 76%, specificity 77%, AUC 0.77; L2/L3: $n = 231$, sensitivity 86%, specificity 89%, AUC 0.87).[190]

Performance characteristics of the MINI index were assessed in further studies (two retrospective[192,193]; one prospective[189]) as summarized in Supporting Information S3: Table S6. It is anticipated that the number, quality, and size of such studies will increase and allow further evaluation of recommended cut scores and assessment of variation in performance according to macroscopic CD location. In clinical trials with endoscopic assessment at baseline and at trial end, MINI index could be employed at interim time points to guide as to whether patients are benefiting from therapy.

6.2.3 | FC

Of the 253 screened manuscripts, 14 met the eligibility criteria and are included herein (Supporting Information S3: Table S7, Supporting Information S2: Figure S3). The suggested cut-off values for MH in the literature ranged from 100 to 367 µg/g at various time points.[175,176,194–198] To address the aims of this guideline, we sought to identify an optimal FC cut off to predict MH at the end of induction therapy to replace a repeat colonoscopy at this time point. Only one pediatric study in the systematic review directly addressed this question and found that Week 8 FC following induction therapy had moderate correlation with Week 8 SES-CD ($r = 0.46$, $p = 0.02$); while only 1 out of 12 children with endoscopically active disease (SES-CD ≥ 3) had a FC > 200 µg/g, 7 of 11 children with endoscopically inactive disease (SES-CD < 3) had a FC > 200 µg/g demonstrating both the high sensitivity and false positive rate of this cut-off level.[188] A recently published systematic review of noninvasive biomarkers in adults with CD sought to identify optimal FC cut-offs for use in a variety of clinical scenarios, including a level below which endoscopic assessment may be avoided; a cutoff of 150 µg/g was recommended to optimize the test's sensitivity and specificity at 81% (95% CI: 74%–87%) and 72% (95% CI: 61%–81%) respectively.[199]

A subset of studies sought to understand if disease location impacts the association between FC and endoscopic activity. Though one study found no statistically significant differences in FC levels based on CD location,[176] all remaining studies concluded that FC levels are higher in patients with active colonic involvement compared to those with isolated ileal disease, and as a result, lower cut-offs should be considered.[188,194,200]

6.2.4 | IUS

Of the 428 screened manuscripts, eight met the eligibility criteria and are included herein (Supporting Information S3: Table S8, Supporting Information S2: Figure S3). BWT, BWS, increased vascularity indicated by color Doppler signal (CDS), and inflammatory mesenteric fat (i-fat) are the most common individual IUS parameters used to assess the presence of inflammation.[201] In an expert consensus, sonographic transmural remission in adults was defined as BWT ≤ 3 mm and the absence of CDS.[202] As recently reported in an initiative to refine existing scoring systems for use in clinical trials, expert local and central reader inter-rater reliability for BWT, CDS, i-fat, and length of the affected segment ranged from moderate to almost perfect.[203] Importantly, central reading was associated with numerically similar or greater reliability estimates compared with point-of-care assessment.[203]

In addition to measurement of individual parameters, IUS disease activity indices have been developed to formalize sonographic CD assessment, including the International Bowel Ultrasound Group-Segmental Activity Score (IBUS-SAS) and the Simple Ultrasound Activity Score for CD (SUS-CD).[204,205]

Supporting Information S3: Table S8 summarizes pediatric studies comparing assessment of intestinal inflammation via IUS versus endoscopy performed contemporaneously, although the maximal interval allowed between procedures varied.[161,165,185,206–209] All but one were single center studies and most were cross-sectional rather than longitudinal. The earliest retrospective analysis simply reported the performance characteristics of IUS in the identification of CD.[161] In subsequent studies, mucosal inflammation visualized at colonoscopy was measured using SES-CD and compared with BWT and/or an IUS disease activity index.[206–210] In general, BWT of a segment increases with greater endoscopic severity in that segment. Particularly in young children, the optimal cut-off of BWT by which to define healthy may be lower than the ≤3 mm agreed upon for adults and adolescents.[165] Studies are ongoing to assess if BWT ≤ 2.5 mm may be a more accurate normalized value for BWT in children.[211]

Two of the pediatric studies included repeated IUS and colonoscopies.[209,210] In the prospective, cohort study of biologic- naïve children initiating anti-TNF or ustekinumab therapy for active terminal ileal CD, a reduction in BWT in the terminal ileum from baseline to Week 8 (either as a percentage or absolute change) was significantly higher in children achieving versus not achieving endoscopic remission.[209]

STARDUST was the first international, multicenter RCT to include a substudy assessing IUS response to treatment.[212] Among adult patients treated with ustekinumab in this phase 3b trial, sonographic response (defined as a reduction in BWT of 25%) and transmural healing (defined as normalization of all IUS parameters) were seen in 46% and 24%, respectively, at 48 weeks.[212] Lack of sonographic response at Week 4 predicted poor Week 48 endoscopic response with a NPV of 73%.[212]

Given the noninvasiveness of IUS and its appeal to pediatric patients, further evaluation of IUS variables, particularly BWT, and of IUS activity indices should occur as part of future clinical trials in children with CD. Along with other noninvasive measures (fecal calprotectin, MINI-index) IUS could replace ileocolonoscopy at the postinduction timepoint, reducing the performance of ileocolonoscopies to baseline and end of study.

6.2.5 | MRE

Of the 261 manuscripts screened, nine met the eligibility criteria and are included herein (Supporting Information S3: Table S9, Supporting Information S2: Figure S3). Active intramural inflammation of CD can exist concurrently with endoscopically demonstrated MH. In a prospective observational cohort study from South Korea, 116 biologic naïve children with CD were re-evaluated by MRE and ileocolonoscopy 1 year after starting anti-TNF.[213] A total of 59% (41/69) of patients who achieved EH (SES-CD < 2) at 1 year exhibited transmural healing, and 91% (41/45) who achieved transmural healing exhibited EH.[213]

Given that colonoscopy allows assessment only of the mucosa, one would not expect perfect agreement between MR tools assessing inflammation transmurally and measures of endoscopic disease. Supporting Information S3: Table S9 summarizes pediatric studies that have attempted to compare MRE and colonoscopy in the assessment of CD activity. As with IUS, early studies examined only the performance of MRE in detecting the presence of CD.[214–216] Others assessed MR-based measures of inflammation such as the magnetic resonance index of activity (MaRIA), simplified MaRIA (MaRIAs), and the pediatric inflammatory Crohn's MRE index (PICMI) in comparison to SES-CD.

The MaRIA has become widely accepted as a tool to assess transmural inflammation in adult patients with CD.[217] More recently, a simplified version of the MaRIA (MaRIAs) was introduced, which includes wall thickness, mural edema, fat stranding (mesenteric T2 hyperintensity), and ulcerations.[218] This version does not require intravenous gadolinium-based contrast agents, which have been associated with deposition in the brain. In accordance with the original MaRIA, it still requires the use of rectal enema, which is less acceptable to children. Both MARIA and MARIAs were developed to assess the terminal ileum and all colonic segments, but not small bowel proximal to the terminal ileum.[217,218]

The PICMI was rigorously developed using double radiologist global assessments of inflammatory activity as the gold standard, validated, and its performance characteristics evaluated in the international, multicenter, prospective ImageKids study.[191] Scoring includes the entire small and large intestine, does not require rectal enemas, and the final score does not include enhancement as a variable, meaning that gadolinium is not required for PICMI calculation.[191] PICMI correlated well with the radiologist's global assessment ($r = 0.85$). Interobserver and test-retest reliability were high (ICC: 0.84; 95% CI: 0.79–0.87; and 0.81, 95% CI: 0.65–0.90, respectively; both $p < 0.001$). In the validation cohort, the performance of PICMI surpassed that of MaRIAs. Excellent responsiveness was found at repeated visits ($n = 116$ MREs; AUC 0.96; 95% CI: 0.93–0.99). Transmural healing was defined as PICMI ≤ 10 and response as a change of >20 points with excellent discriminative validity (AUC: 0.96; 95% CI: 0.93–0.99).

PICMI is validated, and readily available for use as an outcome measure in clinical trials as an assessment of transmural healing. MRE is more time-consuming and less patient-appealing in comparison to IUS, but it is more standardized and intuitive for central reading. MRE is less feasible in young children who require sedation. In this young age group IUS may a preferable substitute to MRE.

7 | PART-IV

7.1 | Colonoscopies in clinical trials

This discussion is based on the previous sections of this manuscript including the systematic review outlined above regarding sigmoidoscopy versus full colonoscopy in UC (Supporting Information S3: Table S4, Supporting Information S2: Figure S1).

In children, ileocolonoscopies pose a particular burden, with the routine use of general anesthesia,[6] and bowel preparation associated with significant anxiety and discomfort. Significant barriers exist with

24 h of a clear liquid diet and adverse symptoms associated with bowel preparation including nausea and vomiting, poor sleep, abdominal pain and fatigue. Not many children and caregivers accept two full ileocolonoscopies in 3 months and this is especially true in the youngest children, the same age group which trials need the most. All regulatory pediatric RCTs face the challenge of small sample sizes for children with a body weight under 30 kg, a crucial group for understanding the dose-exposure relationship. To that end, there is an inverse association between the extent to which a study design deviates from clinical practice and enrolment rate. Furthermore, the high burden of frequent ileocolonoscopies may skew the demographic of trial participants toward older children and adolescents, thereby exacerbating the underrepresentation of the younger and lighter-weight cohort. This imbalance can worsen the generalizability of the trials' findings, particularly regarding dosing in younger children.

Moreover, postinduction Week 12 colonoscopy is not vital, since efficacy should be extrapolated from adults and may be benchmarked by postinduction noninvasive markers, and endoscopic evaluation at 54 weeks. In fact, once accepting extrapolation for efficacy, the procedure may even be considered unethical. Indeed, there is a wide global agreement across pediatric gastroenterologists and professional organizations (ESPGHAN, NASPGHAN, European Crohn's, and Colitis Organization [ECCO], Pediatric IBD network [PIBDnet]) that annual bowel cleanouts, required for full ileocolonoscopy, may be required at most twice in 1 year: at baseline and at trial end,[21,26,28] while in UC, three sigmoidoscopic evaluations may be feasible.

8 | CONCLUSION

Multiple IBD drugs are currently being investigated in clinical trials in adults, for which pediatric planning is still in its infancy (Table 1, Figure 1). While it is paramount to achieve a precise and comprehensive approval process for new drugs in pediatric IBD, it is equally important to expedite the process, so children and adolescents are not denied effective treatment available for adults with IBD (Box 2). By systematically reviewing the evidence of the underlying biology, response to treatments, noninvasive endpoints, PK, and safety, we conclude that a balanced and pragmatic approach is essential. This would require: (1) accepting extrapolation of efficacy and safety data from adults to children 2 years and older; (2) accepting extrapolation of pharmacokinetics to adolescents; (3) incorporating noninvasive postinduction monitoring with at most two ileocolonoscopies per year; (4) avoiding subtherapeutic interventions in studies, including placebos; and (5) minimizing washout and screening period (Figures 2 and 3).

Under these assumptions, future trial designs should be single-arm and open-label to focus on dosing and pharmacokinetics in children weighing <30–40 kg while mandating long-term safety registries, disease- and not necessarily drug-specific. Data should be supported by meticulously collected real-world evidence. Pediatric data must be collected as soon as a confident signal of efficacy and safety is achieved in adult studies. That generally means going into planning no later than phase 2 adult trials and initiating the pediatric trial immediately after the completion of the adult phase 3 trial. Pharmaceutical companies, healthcare providers, families, and regulators must commit to expedite pediatric drug approval. This will resolve the current paradox in which children have the most severe and extensive disease and the highest efficacy of drugs, yet very limited access to these drugs.

ACKNOWLEDGMENTS

The authors would like to thank Andrew Mulberg, Nerissa Velazco, Jan Taminiau, James Canavan, Jennifer Thompson, the Porto pediatric IBD group and others for providing insightful comments on the manuscript and Katharina Ikrath from ESPGHAN's office for organizing the voting platform.

CONFLICT OF INTEREST STATEMENT

Dan Turner—last 3 years received consultation fee, research grant, royalties, or honorarium from Janssen, Pfizer, Shaare Zedek Medical Center, Hospital for Sick Children, Ferring, Abbvie, Takeda, Prometheus Biosciences, Lilly, SorrisoPharma, Boehringer Ingelheim, Galapagos, BMS, AlfaSigma. Jeffrey S. Hyams—last 3 years Advisory Board Janssen, Abbvie, Lilly, consultant Genentech, Pfizer, Takeda, Boehringer Ingelheim, BMS. Holm H. Uhlig supported by NIHR Oxford Biomedical Research Centre, and The Leona M. and Harry B. Helmsley Charitable Trust and has received last 3 years research support or consultancy fees from J&J, Eli Lilly, BMS Celgene, Falk Pharma. Lissy de Ridder—last 3 years received consultation fee, research grant, or honoraria from Abbvie, Janssen, Lilly, Takeda, Pfizer, Medtronics, Alvotech. Marina Aloi—last 3 years received honoraria or consultation fee from AbbVie, Pfizer, Nestle, Sandoz, Takeda Marla C. Dubinsky received consultant fees from Abbvie, Abivax, Astra Zeneca, BMS, Celltrion, Eli Lilly, Genentech, Janssen, Johnson and Johnson, Merck, Pfizer, Prometheus Biosciences, Sanofi, Spyre, Takeda Anne M. Griffiths—last 3 years received consultation fee, research grant, royalties or honoraria from Abbvie, Janssen, Lilly, Merck, Pfizer, Shaare Zedek Medical Centre, SickKids Hospital, Takeda Javier Martín-de-Carpi—last 3 years received consultation fee, research grant, or honorarium from Abbvie, Adacyte, FAES, Ferring, Janssen, Lilly, Nestlé Health Science and Pfizer. Eytan Wine—last 3 years received consultation fees or honoraria from Janssen, AbbVie, Nestle Health Sciences, Pfizer, BioJamp. Richard K. Russell—last 3 years received

consultation fee, research grant, royalties, or honorarium from Janssen, Pfizer, Ferring, Lilly, Amgen, Celltrion and Nestle Health Sciences. Jeremy Adler—last 3 years has received research funding from Janssen Research & Development, LLC.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Turner D, Assa A, Malham M, et al. Reshaping study design for faster extrapolation-based drug approval in pediatric inflammatory bowel diseases: An ESPGHAN–NASPGHAN position paper. *J Pediatr Gastroenterol Nutr*. 2025;1-28. doi:10.1002/jpn3.70275