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Clinical trials and young adults with inflammatory bowel disease

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ABSTRACT

Young adults (approximately 18–35 years) with inflammatory bowel disease (IBD) represent a distinct demographic with unique developmental and physiological characteristics, yet they are underrepresented in clinical trials. This commentary synthesizes insights from a roundtable discussion facilitated by the Crohn's and Colitis Young Adults Network (CCYAN) between young adult patients with IBD and medical professionals, including physicians, nurses, psychologists, and trainees/medical students. Themes include defining young adults as a distinct demographic in research, improving outcomes for young adults with IBD through age-specific data disaggregation, barriers for participation and post-trial responsibilities, as well as regulatory and legislative policy opportunities to enhance young adult representation in clinical trials.

Introduction

Medication trials play a pivotal role in shaping treatment decisions for patients, families, and healthcare providers. Randomized controlled trials, considered the gold standard, randomly assign patients to different treatment groups, including placebo groups, to minimize unmeasured confounding. These trials are instrumental in determining the efficacy and safety of treatment options. However, the demographic composition of clinical trial participants often does not reflect the diverse range of patients seen in real-world healthcare settings.[1,2] Many clinical trials impose exclusions based on disease severity, comorbidities, specific disease locations (e.g., limited proctitis or fistulas), and age extremes, leaving a significant portion of the population underrepresented.

Young adults, in particular, may benefit from increased representation in clinical trials and greater data disaggregation. This age group is uniquely positioned due to ongoing physiological changes, such as hormonal fluctuations and immune system maturation, which may influence treatment responses, adherence, and experiences of adverse events. Despite these critical considerations, young adulthood remains poorly defined in clinical research. Age ranges used to define young adults vary widely across IBD-related studies and among regulatory agencies, further complicating the integration of findings.

Recognizing these gaps, we convened a patient-led roundtable that brought together patients, physicians, researchers, and care partners to examine the challenges and opportunities for young adults in clinical trials. Several challenges were identified during the roundtable, including the lack of reporting disaggregated result information from

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young adults. Without subgroup analysis, it is difficult to discern potential differing outcomes for young adults with IBD compared to their older counterparts. This may be particularly important in young adults who may still be experiencing hormonal and immune system changes that influence their health and treatment efficacy. Further complicating this is that young adulthood is not well-defined, and traditional age definitions and cutoffs for young adults depend on the individual disease group studied. As such, significant heterogeneity in the age ranges has been reported across IBD-related studies and among regulatory agencies.

Defining young adults as a distinct demographic in research

Despite the peak of IBD occurring during adolescence,[3] young adults only make up a small proportion of individuals enrolled in clinical trials. The pediatric trials tend to miss older patients who may have transitioned to adult care, while the adult trials tend to miss younger patients. As a result, the 18-—to 35-year-old age group is underrepresented in many studies. Adults ages 36–75 (odds ratio 1.68, 95 % confidence interval 1.46–1.92) were substantially more likely than those ages 18–35 to participate in a randomized clinical trial to treat inflammatory bowel disease.[4]

A major challenge is the lack of a global consensus on defining the young adult patient demographic and recognizing it as a distinct and unique period of development.

Patients under 18 are generally classified as pediatric, a category with clearly defined age parameters established by the International Council for Harmonization (ICH) and the World Health Organization (WHO). However, no such standardized definition exists for young adults. The ICH E11 (R1) guidelines suggest that age classification should be based on pharmacology and developmental biology rather than arbitrary age cutoffs, but this principle has not been uniformly applied to young adults in IBD research.[5]

Even defining adolescents, a closely associated age group with young adults, varies among organizations. The US Food and Drug Administration (FDA) defines adolescents as individuals aged 12 through 21 (up to but not including the 22nd birthday),[6] while the World Health Organization (WHO) defines them as those between 10 and 19 years.[7] This gray area of a standard definition for the young adulthood age range beyond pediatrics makes it challenging to identify this subgroup within a specific patient category and provide tailored care.

In oncology, adolescents and young adults (15–39) have been marked as a special population by agencies such as the Government Accountability Office,[8] even having separate guidelines through the National Comprehensive Cancer Network.[9] However, even within this, there is a push to have public data disaggregated by individual participant data.

While individuals aged 18–26 are often considered young adults,[10] chronological age alone is an insufficient marker of development, particularly in individuals with delayed pubertal, physical, or cognitive development. This age group requires more precise consideration in clinical trials. By focusing on key developmental factors, such as physical and cognitive changes, researchers can better capture the unique impact of therapeutic interventions on individuals in their early 20 s. It is essential to recognize that chronological age is an imperfect metric for measuring development, as it varies significantly between individuals.

Improving outcomes for young adults with IBD through age-specific data disaggregation

Including biological and cognitive age measures in clinical trials may advance our understanding of drug disposition, but as an initial step, disaggregating the chronological age segments, particularly for young adults, can help discern certain safety and efficacy signals.

Oncology offers valuable lessons in the importance of data disaggregation. For instance, the National Childhood Cancer Registry mandates data reporting in five-year increments, allowing differential outcomes by age group to be identified.[11] Similarly, the *Surveillance, Epidemiology, and End Results* (SEER) database uses 5-year relative survival as a surrogate outcome.[12]

In contrast, IBD-related clinical trials often fail to publicly report outcomes or safety data stratified by age, even when young adult participants are included. For example, in the UNITI 1 and 2 trials evaluating ustekinumab in Crohn's disease, 24 % of participants were aged 18–24. However, their outcomes were not analyzed or reported by age.[13] This omission limits the ability to determine subgroup-specific safety and efficacy, leaving unanswered questions about whether younger adults may experience different therapeutic benefits or adverse event rates compared to older patients. Further progress could be achieved by designing clinical trials specifically for young adults or by conducting qualitative research to understand their experiences engaging in clinical trials. Such insights could inform the development of clinical trials better tailored to the needs of this demographic.

Additionally, differences in disease activity measures between pediatric and adult care further complicate efforts to assess young adults. While validated endoscopy scores are now used in clinical trials, patient-reported outcomes (PROs) validated for older adults may lack relevance for younger adults. Measures such as treatment adherence, social functioning, and readmissions may vary in significance depending on the population. Likewise, measures for acute lung injury illustrate how differing classification systems can lead to discrepancies in disease severity assessments for young adults, depending on whether pediatric or adult metrics are applied.[14]

Scoring systems that are not thoughtfully designed risk creating inconsistencies in how patients are assessed, potentially impacting treatment decisions and the criteria for inclusion in clinical trials. To ensure accuracy and relevance, disease activity measures and patient-reported outcomes must be explicitly validated for the subgroup of interest.

Young adults with IBD may also exhibit a different disease phenotype than children and older adults, but this information would not be known without adequate enrollment rates or appropriate subgrouping. Several studies have demonstrated that adolescents have more aggressive and extensive IBD than children who were diagnosed at a younger age. For example, adolescents with Crohn's disease are more likely to develop disease complications like fistulas than younger children.[15,16] Young adults are also more likely to develop these complications than older adults.[17] During our roundtable discussion, one participant questioned whether this was because there might be a distinctly longer time to diagnose in adolescence. A delayed diagnosis is associated with disease progression in Crohn's disease and increased rates of intestinal surgery in both Crohn's disease and ulcerative colitis.

Furthermore, other studies have found that there is more extensive[18] colitis in children than in adults and more acute[19] colitis in adolescents than in younger children. It is important to identify this for young adults with IBD as well. One physician at our roundtable session suggested that rapid immune system changes during young adulthood might underlie these phenotypic differences. To adequately understand a differing phenotype, it would be important to have adequate enrollment rates for young adults in clinical trials, a challenge noted by numerous studies, including one looking at age-based[20] differences in IBD.

Barriers for participation and post-trial responsibilities

Young adult patients, care partners, and care providers at our roundtable identified unique challenges in ensuring ethical, informed consent processes for adolescent populations. Adolescents are often at a developmental stage where their autonomy and perspectives must be considered alongside parental involvement in the consenting process for research participation. Balancing the need for confidentiality and autonomy with the requirement for informed assent of adolescents and consent from their parents or caregivers can involve nuanced and sometimes difficult decision-making. Counseling on the risks and

benefits of experimental therapies is complex when engaging with adults, but these challenges are amplified when adolescents and their parents are joint decision-makers.

Trust emerged as a critical factor in addressing these challenges. During our roundtable discussion, young adult patients emphasized the importance of having a designated contact person within the study team who they could approach with concerns about treatment side effects or for additional information. This direct line of communication complements the ability of parents or guardians to communicate with the study team and encourages transparency. Study teams must clearly outline how information will be shared and with whom, ensuring clarity and minimizing confusion between guardians and adolescents. This 3-way relationship should be fostered during the recruitment stage and continued throughout the length of the trial. This easily accessible communication ensures that the ongoing decision to remain in the trial is as informed as possible despite the inevitable uncertainties of clinical trials.

Building on this foundation of trust and clear communication, clinicians play a critical role in ensuring that young adult patients understand that their health comes before the trial's success. Young people may feel greater pressure to remain in a trial for the sake of the project or to satisfy adults in their lives, such as parents or clinicians. To mitigate this pressure, deliberate conversations should reinforce that patients can withdraw from a trial at any time if it negatively impacts their health. Furthermore, young adult participants should be clearly informed about how their data will be used and when they will gain access to it. While precise timelines may be difficult to provide at the start of a trial, transparency regarding when treatment outcomes will be unblinded and when trial results may become available is crucial. This is especially important for adolescents and young adult patients whose life circumstances often change rapidly, such as starting higher education, finding employment, or moving out of their parental homes, and who may require additional information to plan for their futures.

Compensation for participation in clinical trials is a common practice and serves as an incentive for recruitment. However, compensation for participation varies from trial to trial. Young adult patients at our roundtable noted the lack of travel-related compensation as a significant barrier to participation. In many cases, the cost of travel offsets any financial compensation provided for participation, creating a negative impact on their overall experience. Roundtable participants recommended that all trials offer some form of compensation, regardless of their type or purpose. When financial incentives are not feasible, alternative motivators, such as access to data or other meaningful benefits, should be considered to encourage participation.

Another significant challenge identified by roundtable participants was the gap between pediatric and adult trial centers, which can result in a loss of follow-up as young adults transition to adult care. To address these issues, participants recommend establishing trust and accountability through accessible communication, ensuring patients and families have a clear understanding of data usage and timelines, and creating joint Institutional Review Boards (IRBs) to support seamless transitions between pediatric and adult care systems. By incorporating these recommendations and prioritizing the perspectives of young adult patients, researchers can ensure adolescents' ethical and effective participation in clinical trials, ultimately improving the quality and relevance of research in this important population.

Regulatory and legislative policy opportunities to enhance young adult representation in clinical trials

To enhance transparency and inclusivity, clinical trial sponsors should be required to report raw data publicly, and companies should not allow for selective data publishing. Additionally, further exploration is needed to define young adults as a distinguished demographic, drawing lessons from oncology reporting standards (ages 15–39) and refining these age parameters for IBD to reflect its unique characteristics better. Understanding the specific needs of young adults in clinical trials is critical to tailoring research and ensuring that this group is effectively represented.

The NIH, FDA, and other organizations have been working to improve inclusion in clinical trials, but progress has been slow and incremental. Several legislative acts have sought to encourage the inclusion of women and minorities in clinical trials, such as the Revitalization Act in 1993, the Best Pharmaceuticals for Children Act in 2002, and the Pediatric Research Equity in 2003, each of which attempted to encourage pharmaceutical companies and others to include children in research. Most recently, the 21st Century Cures Act has aimed to broaden the research portfolio to incorporate randomized trials and allow the use of real-world data for regulatory approval.

When thinking about young adult patients, roundtable participants offered several key policy and legislative recommendations, including advocating for the FDA to require the public reporting of disaggregated data, including post-hoc analyses of age subgroups. Additionally, participants suggested lobbying Congress to prioritize adolescents and young adults in efforts to increase clinical trial diversity. One promising avenue for these policy changes is through the Prescription Drug User Fee Agreements, a recurring piece of legislation passed every five years to fund essential FDA activities. These measures could help ensure young adults are better represented in clinical research and that their unique needs are addressed in future trials.

Conclusion

The absence of a standardized definition for the young adult age group, coupled with their underrepresentation in clinical trials, poses significant challenges in understanding the unique needs of this demographic in managing IBD. Data disaggregation by age could reveal crucial differences in drug efficacy, safety profiles, and adverse events specific to this age group. Additionally, this roundtable discussion highlighted the need for age-appropriate disease activity measures and patient-reported outcomes and to address ethical considerations in the consent process for adolescent participants. Barriers to participation, such as inadequate travel compensation and gaps between pediatric and adult care centers, must be addressed to improve representation. Moving forward, regulatory and legislative actions must be taken to enhance the inclusion and proper analysis of young adults in IBD clinical trials, ensuring that this population receives the most appropriate and effective treatments based on evidence specific to their developmental phase.

Ethical Statement

Human rights

This article does not contain any studies with human participants performed by any of the authors.

Informed consent

This article does not involve human participants, so informed consent was not required.

Welfare of animals

This article does not contain any studies with animals performed by any of the authors.

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Declaration of Competing Interest

The authors do not have conflicts of interest.

Data availability

No data was used for the research described in the article.

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