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Celiac Disease Clinical Trials

Barriers and Strategies *for* Recruitment and Retention

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Introduction

Celiac disease is a chronic, immune-mediated enteropathy triggered by gluten ingestion that affects approximately 1% of the population worldwide[1]. Despite strict adherence to a gluten-free diet being the only accepted treatment, many patients experience persistent symptoms, impaired quality of life[2], and ongoing intestinal injury[3]. These limitations underscore the urgent need for novel therapeutics that can prevent or reduce the symptoms or small intestinal damage caused by gluten exposure. Over the past decade, the number of investigational agents targeting celiac disease has grown[4]; however, clinical trial execution in this population remains challenging.

Patient recruitment is a well-documented bottleneck in gastrointestinal and rare disease research, but celiac disease poses unique obstacles. Strict dietary management may reduce patients' motivation to participate in placebo-controlled studies requiring gluten consumption, and variable disease awareness among providers can constrain referral pipelines. Additionally, research site infrastructure and operational workflows influence trial performance, including the speed of patient identification, response to referrals, and follow-up engagement.

To address these issues, the Celiac Disease Foundation developed iQualifyCeliac™ — a digital recruitment and referral tracking platform designed to connect eligible participants to clinical trials while providing sites with recruitment support and operational metrics.

Given the use of iQualifyCeliac™ across a number of celiac disease clinical trials, there is an opportunity to gather valuable site perspectives on how the platform can complement other recruitment strategies and inform approaches to optimize patient identification and engagement.

Understanding barriers and facilitators to efficient patient enrollment is essential to accelerating therapeutic development for celiac disease.

Prior research on recruitment in other conditions suggests that trial success depends on a combination of organizational capacity, investigator engagement, and patient-centered recruitment strategies[5], but these insights have not been systematically examined within the celiac disease trial landscape. Identifying actionable strategies could improve recruitment yield, optimize resource allocation, and shorten development timelines for new therapies.

This study aimed to explore the site-level factors influencing recruitment and retention in celiac disease clinical trials across the United States.

Using a mixed-methods approach, we conducted in-depth interviews of principal investigators and site coordinators, with the goal of characterizing barriers and facilitators to trial participation, and generated practical recommendations to improve the design and implementation of future celiac disease clinical research.

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Methods

Study Design

This study employed a mixed-methods design combining descriptive quantitative and qualitative content analysis to explore factors influencing the success of celiac disease clinical trials across research sites in the US.

Data were drawn from in-depth interviews with site leadership to provide direct experiential insights categorizing barriers and facilitators to patient recruitment and retention.

Interview findings were then utilized to inform a set of recommendations to strengthen site-level practices supporting patient engagement and study success.

Site Selection & Participants

Prospective clinical research sites were identified using data collected in the Celiac Disease Foundation's iQualifyCeliac™ clinical trial recruitment and referral tracking platform. Available data were analyzed to compare metrics such as average referral response time, participant enrollment and completion rates, and referral conversion rates, to establish a spectrum of clinical trial performance.

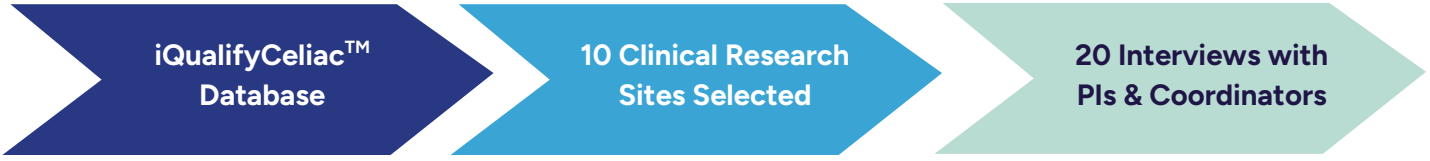
Email invitations were distributed broadly to 47 sites who met our inclusion criteria:

- Previous participation in one or more celiac disease clinical trials
- Experience recruiting with the iQualifyCeliac™ platform

Those expressing interest were considered, with the goal of enrolling 10 sites, each required to provide one principal investigator and one site coordinator to ensure both clinical and operational perspectives were represented.

Ten sites were selected on a rolling basis until the target sample was reached, using a purposive sampling approach to capture a range of site performance.

Four additional sites communicated interest but were either not able to provide both site representatives, or provided a response after the enrollment period ended. All participants consented to the audio/video recording of interviews and anonymized use of their responses.



Methods

Data Collection

Semi-structured interviews were conducted between July and September of 2025 via one-on-one video conferencing.

Principal investigators and site coordinators were interviewed separately to encourage open discussion and to minimize potential response bias that could arise from shared participation.

Each session lasted approximately one hour and followed a structured guide containing open-ended questions tailored to the respondent's role. A single interviewer facilitated all sessions to ensure consistency in tone, format, and follow-up. Interview recordings were transcribed verbatim by a professional third-party service. Four researchers independently reviewed transcripts, extracting responses corresponding to each question set. Summaries were created to condense response data into key insights while preserving participants' original meaning. A final review by a single team member was conducted to ensure consistency and coherence across the dataset.

Quantitative & Qualitative Analysis

Descriptive statistics were calculated for select interview responses, including closed-ended questions, counts, and categorical questions. Quantitative data were summarized using counts, percentages, means, medians, standard deviations, and ranges as appropriate.

Qualitative data were analyzed using deductive and inductive content analysis. One researcher independently generated an initial code list by open coding the transcript excerpts/summaries. Two additional researchers independently reviewed coding, followed by iterative discussions to refine categories and resolve discrepancies. Coding focused on identifying both unique experiences and recurring patterns related to recruitment strategies, participant engagement, and trial execution.

Final themes were developed through consensus review, categorizing barriers and strategies for recruitment and retention to provide a comprehensive understanding of factors influencing trial performance.

Results

Sample Characteristics

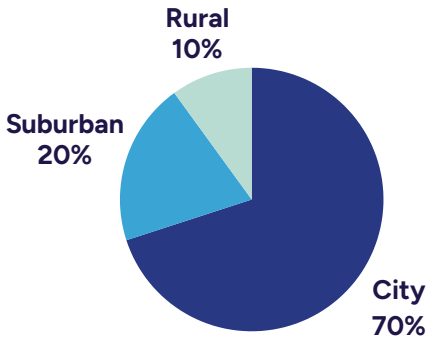
In total, 21 clinical research site leaders were interviewed, with 20 participants included in the analysis, consisting of **10 principal investigators and 10 site coordinators.** One additional site coordinator was interviewed; however, their data were excluded to avoid missing corresponding data from the site's principal investigator who was unable to participate.

Demographic and professional characteristics of the interview participants, as well as the study sites, are presented in Tables 1a–1c.

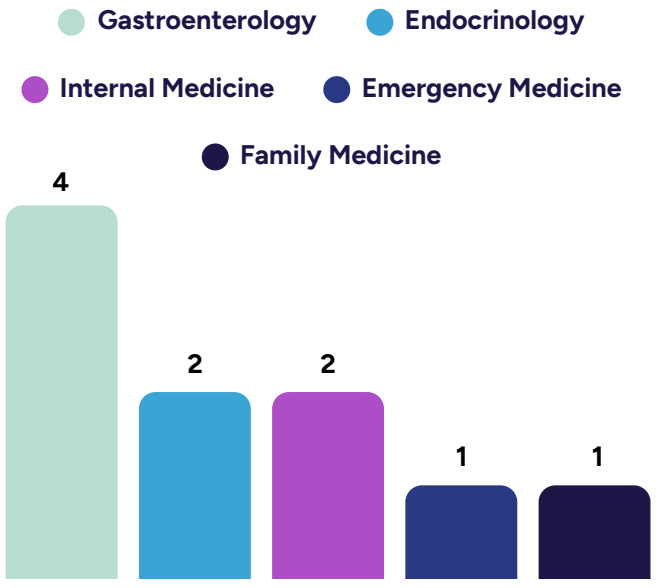
Principal investigators varied widely in years of site experience (mean 14.5 years; range, 2–30), reflecting a mix of early-career and highly experienced leaders. These clinicians predominantly specialized in gastroenterology followed by endocrinology and internal medicine, providing perspectives from a variety of clinical backgrounds.

Site coordinators similarly brought diverse experience, with tenure at their current sites ranging from 2 to 20 years (mean, 7; SD, 5.5). Involvement in patient recruitment varied, with half directly conducting referral outreach, while the remainder either strictly oversaw recruitment, or provided a combination of oversight and individual contribution.

Study site characteristics were heterogeneous: only half reported a primary focus on digestive disorders or celiac disease, while the remaining sites generally conduct studies enrolling broader or more differing patient populations. Geographically, the 10 sites were spread throughout the US, with the majority located in urban settings.



Study Site Locations



Principal Investigator Specialty

Table 1a. Research and Celiac Disease Trial Experience of Interview Participants, **Principal Investigators**

Participant Demographics	Total N=10*
Experience at Current Site, years	
Mean (SD)	14.5 (11.3)
Min-Max	2-30
Clinical Specialty, n (%)	
Gastroenterology	4 (40.0)
Endocrinology	2 (20.0)
Internal Medicine	2 (20.0)
Emergency	1 (10.0)
Family Medicine	1 (10.0)
CeD Studies Over Career	
Mean (SD)	3.8 (3.1)
Min-Max	1-10
CeD Studies Conducted at Current Site	
Mean (SD)	3.6 (3.1)

*Included one Sub-Investigator who was closely involved with the study, in place of the Principal Investigator.

Table 1b. Research and Celiac Disease Trial Experience of Interview Participants, **Site Coordinators**

Participant Demographics	Total N=10
Experience at Current Site, years	
Mean (SD)	7 (5.5)
Min-Max	2-20
Recruitment Involvement, n (%)	
Directly performs recruitment tasks	5 (50.0)
Oversees recruitment	2 (20.0)
Combination, oversees and contributes	3 (30.0)
CeD Studies Over Career	
Mean (SD)	2 (1.3)
Min-Max	1 - 5
CeD Studies Conducted at Current Site	
Mean (SD)	2.2 (1.0)

Table 1c. Study Site Characteristics

Participant Demographics	Total N=10
Digestive Disorder or Celiac Disease Focus, n (%)	
Yes	5 (50.0)
No	5 (50.0)
Location Type, n (%)	
City	7 (70.0)
Suburb	2 (20.0)
Rural	1 (10.0)
Average Workload, studies*	
Mean (SD)	12.3 (14.8)
Min-Max	4-50

*Question did not specify total active studies versus currently enrolling, therefore there was some fluctuation in response type; if response given was a range, median value was used.

Recruitment Barriers

Principle Investigators

Across sites, **principal investigators** reported a range of barriers affecting patient enrollment into celiac disease trials. The gluten challenge was most frequently cited as an activity that deters many eligible participants due to symptom recurrence and perceived burden.

One principal investigator reported that gluten challenges during the screening or run-in periods were particularly detrimental to recruitment success.

> ***There was a gluten challenge before randomization, and that was a barrier to enrollment when that existed, so we had expressed the difficulties with that. They reformulated the protocol, and they took that away, which made [enrollment] easier. (PI-B)***

Additional obstacles largely fell into two groups, stringent inclusion/exclusion criteria (including: diagnostic biopsy requirements, diagnosis specificity, and gluten-free diet requirements), and patient burden (including: time commitment, travel, visit frequency/duration, and contraception requirements).

Site Coordinators

Site coordinators also reported a variety of barriers hindering patient enrollment in celiac disease clinical trials. The gluten challenge was the most frequently cited deterrent, noting a reluctance from patients to risk symptom recurrence.

Coordinators reported additional trial design features posing obstacles for recruitment, such as early-phase studies and the possibility of placebo assignment – which could discourage participation among otherwise interested patients.

One coordinator pointed to a patient misconception that "first-in-human" implies an absence of any prior testing, indicating a gap in knowledge regarding the preclinical research process and safety evaluation required before FDA authorization of Phase 1 trials.

Half of coordinators also emphasized administrative barriers, particularly delays in obtaining outside medical records or pathology reports to confirm eligibility, which could slow screening or lead to exclusion altogether, if records could not be located.

Coordinators overwhelmingly reported that the patients they encountered did not voice concerns about compensation, suggesting it was infrequently a barrier to this highly motivated population.

However, a number of logistical burdens posed challenges, including frequent or lengthy visits, travel demands, and limited flexibility in scheduling, particularly where only standard clinic hours were available. For example, one coordinator stated,

> ***...there were definitely people who just couldn't take that much time off and couldn't participate solely because of the study schedule. (SC-H)***

Another factor influencing recruitment was variability in referral outreach. While some sites made numerous, persistent attempts to reach interested participants, others ended outreach sooner, potentially reducing the screening pool.

Coordinators also noted that some referrals (age dependent) are less responsive to certain communication methods (i.e., phone, email), suggesting the reliance on a single or less strategic mode of contact may fail to engage all potential participants effectively. Several went on to suggest that many of their patients and community members were unlikely to answer a phone call from an unknown number.

Recruitment Strategies

Principle Investigators

When it came to the initial step of improving clinical trial awareness, **principal investigators** most frequently pointed to utilizing the Celiac Disease Foundation for referrals as a successful recruitment strategy.

Other commonly reported strategies for targeting this patient population centered around in-person interactions like outreach to local businesses, participating in community/educational events, and relying on word-of-mouth.

One principal investigator shared that, in addition to speaking to patients about research opportunities during regular clinic visits,

> ***...we go one step further. We have a QR code in every patient room which tells them that we have studies. So, whilst they are waiting to see me, they can scan the [QR code]. (PI-H)***

Once a patient's interest was piqued, investigators found it helpful to communicate clear safety measures and set accurate expectations about study activities to ease concerns. This included emphasizing that participants may withdraw from the study at any time, clarifying that activities are conducted under close medical supervision, and reinforcing that they are otherwise expected to maintain their gluten-free diet throughout the study.

Investigators also highlighted that the gluten challenge involves precisely measured amounts of gluten, ensuring exposure is carefully controlled. These discussions directly addressed common misunderstandings and assumptions patients may initially form about clinical trials.

For example, one principal investigator highlighted the value of a visual aid to a patient's impression of study activities and the overall commitment, noting that,

> ***Some consent forms just [list] each visit and what's happening. But if you have a chart that shows how many [visits], which weeks they have to come, that helps a lot too as far as scheduling. (PI-A)***

In addition, several principal investigators noted that increasing one-on-one time spent with patients, on their part, was integral when it came to easing concerns.

Site Coordinators

Site coordinators described several practical strategies they found effective for improving enrollment in celiac disease clinical trials. There was consensus across sites that rapid outreach to referrals was crucial for maintaining patient interest in trials and subsequent conversion to enrollment. Many sites emphasized contacting potential participants within 24–48 hours.

Notably, about half of coordinators recommended extending outreach beyond three attempts before considering a referral unreachable.

Coordinators emphasized the value of adapting communication methods to participant needs, noting that younger individuals often responded best to text messaging, while older participants were more reliably reached by phone. Those observing that many individuals no longer answer calls from unfamiliar numbers underscored diversified outreach attempts as especially important.

One coordinator described their site's targeted efforts to adapt to referrals' schedules,

> ***[We] do these things called call nights where we stay late and work from 5:00 p.m. to 7:00 p.m. just making calls to people that might be working during the day. And then, we do have some of the recruiting staff that does come in on the weekends [to] try to get ahold of people. (SC-B)***

Preparing and educating patients early was viewed as essential. Coordinators described providing clear, proactive information about study expectations, sending informed

consent documents in advance to allow thoughtful review, and involving principal investigators directly to answer questions and build trust.

As a part of these early conversations, two recommendations stood out for their appeal to patient motivations and the clinical setting.

One coordinator shared their site's unique approach to justifying the gluten challenge, where the principal investigator routinely explains, **"that they're going to be exposed to gluten in real life anyway" (SC-D)**, so wouldn't they prefer an environment with medical supervision and support.

Several others stressed the value of additional health care, pointing out to referrals that studies often offer closer monitoring and health insights than their standard care.

The importance of internal preparedness was also stressed, including early review of referrals and ensuring a shared understanding of inclusion and exclusion criteria among staff.

When recruitment lagged, coordinators described adjusting their approach, such as refining marketing strategies to better reach the target population, expanding community awareness through social media and local networks, and engaging patient advocacy groups or referring providers to increase reach. Collectively, these strategies were viewed as central to maintaining recruitment momentum.

Retention Barriers

Principle Investigators

Principal investigators resoundingly reported that they experienced few barriers to retention, with little-to-no dropouts in celiac disease clinical trials.

Investigators primarily reported barriers that could not necessarily be controlled by site staff, such as adverse events, study duration, reactions to gluten challenges, and life events. However, site visit duration was also identified, which can vary between sites even when following the same trial protocol. Overall, investigators noted these barriers to be the most common, yet infrequent, reasons for withdrawal.

Site Coordinators

Site coordinators also reported few significant challenges with participant retention in celiac disease clinical trials, and several provided no specific concerns.

Among the sites that did describe difficulties, the most frequent barrier was symptom provocation and adverse events in trials with a gluten challenge, which occasionally prompted participants to withdraw. Coordinators also described loss of confidence or waning engagement over the course of a trial if communication with the research team was limited.

A few coordinators noted that struggling with uncertainty about placebo assignment led some patients to consider withdrawal.

More commonly, patients were concerned with the possibility of not receiving treatment, while one coordinator noted that,

> ***...[some] people had accidental gluten exposure outside of the study and they felt, oh, I must have the placebo. And then it can be sometimes hard to retain those people... they're thinking, oh, well, maybe I have the placebo or this isn't working. (SC-J)***

In addition, beginning with unrealistic perceptions of the trial's practical demands, including travel distance and the overall time required to complete study visits, were reported as factors influencing attrition. Overall, these concerns were not reported consistently, suggesting that while retention barriers exist, they were not a prominent challenge across most sites included in this study.

Retention Strategies

Principle Investigators

Owing to the success of trial retention, **principal investigators** reported a variety of strategies for keeping patients feeling confident and connected during their study participation. Tactics most commonly fell under the category of patient engagement and empowerment, including strategic communication, building rapport, demonstrating an appreciation for their contribution, and providing personal health data/results.

Several investigators noted that their sites provide patients with a 24/7 contact method, offering continued support and easing concerns about activities or symptoms they may experience off-site.

The quality of care provided was also a concept several investigators mentioned, suggesting being supportive, accommodating patient needs, and involving nursing staff contributed to their patients' experience.

As an example, one investigator pointed out that addressing the underlying nutritional and micronutrient deficiencies associated with celiac disease demonstrated to patients a deeper level of care and consideration, that,

> ***...as a physician who does work like this, the patient is automatically much more interested in participating because they understand that they're going to get quality care, they're not just a number. (PI-C)***

Another factor which may contribute to their success with patient engagement is the overwhelming impression felt by investigators that patients with celiac disease exhibit higher medical literacy than the average patient seen at each site, regardless of location within the US or urban/rural classification.

Most investigators reported that patients were generally very knowledgeable about their disease and accustomed to invasive testing, so common clinical activities required minimal explanation, though mechanism of action, for example, required a more typical level of explanation.

However, one investigator reported concerns about a frequent level of misinformation shared by patients, that among even those with high medical literacy,

> ***...there's a lot of inaccurate information because people get loads of information on social media, which may not necessarily be completely accurate, but they are very, very clued in on aspects of the disease. (PI-H)***

Finally, the overall way in which the site staff presented themselves emerged as a recurring theme. Throughout interviews, investigators most-often highlighted the importance of professionalism, organization, and friendliness, given their impact on patients' impression of the team and willingness to continue in their care.

Site Coordinators

To support participant retention, **site coordinators** described strategies centered on maintaining connection, reducing burden, and fostering a sense of safety and trust.

Frequent and proactive communication was the most consistently reported approach, with many sites keeping in regular contact between visits to check on well-being and reinforce engagement. Coordinators emphasized the value of a personal relationship between participants and the study team, often providing a direct phone number or even personal cell contact to ensure easy access when questions or concerns arose.

In particular, one coordinator reported a critical step in establishing transparency and healthy lines of communication in case patients feel differently after enrolling,

> ***I also tell them all when I'm going through consents with them, you have the right to withdraw at any time, but if you do want to or if you start thinking about it, please just call us and we can talk about it... (SC-A)***

Flexibility and accommodation were also common themes, with several coordinators highlighting the importance of adapting to

patient needs. Many sites created a comfortable study environment to reduce participant stress, such as providing comfortable furniture, private rooms, gluten-free snacks/meals or kitchen access, Wi-Fi/entertainment, and allowing participants to bring a companion, such as a spouse or child, for support.

Some coordinators described tailoring challenging study activities to individual preferences, when possible, such as offering options for the temperature of water used in the gluten challenge slurry to improve comfort. Others emphasized the importance of clear preparation before and throughout the trial, helping participants to anticipate study demands and normalizing potential symptoms when gluten exposure was required.

Finally, one coordinator also spoke to the impact of study design, suggesting a more patient-centered approach from the protocol could significantly ease concerns and facilitate trial completions,

> ***...[if] there is a crossover design of the trial, that relieves them that, "Yes, if I am probably getting a placebo, [but] there is a chance that I may get switched over to the actual drug." It's not a blind path for them where they do not know whether they were getting the medication or not getting medication. (SC-E)***

Collectively, these strategies aimed to build trust, minimize disruption to daily life, and sustain engagement over the full course of participation.

Celiac Disease Foundation Recruitment

Principle Investigators

Principal investigators widely regarded the Celiac Disease Foundation's recruitment services as a key contributor to successful trial enrollment.

Investigators most commonly noted that the Foundation was 'crucial to the study,' citing greater patient reach, higher enrollment numbers, and more completed participants as directly attributing to trial success. Sites with smaller local patient networks or those newer to celiac disease research found the services especially helpful in expanding outreach beyond their usual capabilities.

As an example, one principal investigator reported,

> ***I think because you guys [referred] 100% of who we've been able to get into the study, I think it's been great working with y'all. I think we'd always be interested in [collaborating with the Foundation]. (PI-I)***

Increased access to qualified referrals and heightened site visibility/credibility within the celiac disease community were cited as the most salient benefits.

Another investigator suggested use of the Foundation's recruitment services allowed them to stand out professionally,

> ***[The] number one benefit was to help our site to become one of the top recruiting sites. (PI-E)***

Investigators also highlighted the iQualifyCeliac™ platform's role in increasing patient awareness of clinical trial opportunities, fostering trust through its association with a well-known patient advocacy organization.

While there was some variability in the reported magnitude of impact across sites—reflecting differences in patient networks and follow-up practices—perceptions were overwhelmingly favorable. Notably, all ten principal investigators indicated they would recommend using the Foundation's recruitment services to other research sites, underscoring the value and contribution to successful patient enrollment.

Site Coordinators

Site coordinators predominantly viewed the Celiac Disease Foundation's recruitment services as a highly valuable supplement to site-level efforts. Nearly all coordinators indicated that referrals from the Foundation's iQualifyCeliac™ platform helped their site reach enrollment targets faster than alternative recruitment methods. Coordinators emphasized that these prescreened referrals tended to be well-informed and highly motivated, often arriving with a clear understanding of trial expectations and interest in research participation. This reduced the time needed to screen and educate patients, and improved enrollment conversion. Coordinators also observed that participants referred by the Foundation tended to be more engaged and had higher completion rates than those recruited through other channels.

While a few noted some variability in referral eligibility and readiness, this was generally seen as infrequent and did not outweigh the overall benefit. Ratings of the Foundation's recruitment support were consistently strong, with a median score of 9 out of 10. Across sites, nine coordinators expressed a preference for trials working with a patient advocacy organization, such as the Celiac Disease Foundation.

As an example, one coordinator shared that the specialized support meant a lot for their recruitment team,

> ***It can be a lonely space on this end sometimes, you know. And so getting the support from [an organization] who is dealing with that particular disease, that indication, I think it's wonderful... (SC-C).***

Overall, site coordinators described collaborations with patient advocacy groups as trusted and effective ways to identify qualified participants while easing the site's recruitment workload.

Discussion

This mixed-methods study provides the first systematic examination of site-level factors influencing recruitment and retention in celiac disease clinical trials.

Through interviews with principal investigators and site coordinators across ten US research sites, we identified key barriers and effective strategies, informing practical recommendations to strengthen patient engagement and enrollment outcomes.

Our findings revealed that while people with celiac disease are highly motivated to participate in clinical trials, recruitment remains challenging due to disease-specific burdens, trial design constraints, and operational variability across sites.

Importantly, this study also highlights the significant impact of coordinated patient advocacy partnerships, such as those with the Celiac Disease Foundation, in facilitating patient trust, accelerating enrollment, and improving completion rates.

Recruitment and Retention Dynamics

The gluten challenge emerged as a primary deterrent to participation, consistent with existing literature noting the activation[6,7] and burden[8] of symptom recurrence in gluten reintroduction trials. Although less common, apprehension about early-phase studies and placebo assignment also posed meaningful barriers.

These findings underscore the need for clear, proactive communication about study safeguards—including controlled dosing, close medical supervision, and regulatory oversight—and transparent education on the scientific rationale for gluten exposure and placebo use to reduce misconceptions and bolster patient confidence.

Operational factors were also reported to play a pivotal role in recruitment outcomes. Sites consistently emphasized that timely outreach was essential to maintaining patient interest, this alignment provided evidence that responsiveness within 24–48 hours of referral may significantly improve enrollment conversion. Equally important was the persistence of follow-up. Sites recommended extending beyond a typical three to four contact attempts before classifying referrals as unreachable.

Given previous recommendations to diversify outreach efforts[9], adapting communication methods to maintain pace with evolving technologies and participant preferences proved critical, as anticipated. Finally, sites highlighted that internal team preparedness and the ability to adapt marketing strategies were central to sustaining recruitment momentum.

Collectively, these findings demonstrate that recruitment success in celiac disease trials relies not only on study design but on operational agility and patient-centered approaches.

Retention challenges were less pervasive but not absent. Reported withdrawals most often occurred in response to symptom provocation during gluten exposure and to waning engagement when study demands proved greater than anticipated or when communication with the research team diminished. Practical burdens, such as travel and time requirements, were mentioned but inconsistently observed.

These findings suggest that retention is generally stable once enrollment occurs, but it benefits from deliberate expectation management and sustained participant support[10].

Patient Advocacy Partnerships

Both investigators and coordinators described the Celiac Disease Foundation's recruitment services as accelerating enrollment, providing participants who were well-informed and highly engaged, and supporting higher completion rates compared with other channels. Although some variation in referral readiness was acknowledged, the broad preference for advocacy-supported trials highlights these partnerships as a valuable, scalable strategy to extend reach and improve trial efficiency.

Given the emphasis principal investigators and site coordinators reported on establishing a relationship with the patient population, this analysis further supports the additional benefit of advocacy-based recruitment that builds on established trust and disease expertise.

The success of the iQualifyCeliac™ platform complements the growing conversation from health engagement literature showing that community-endorsed recruitment channels can be critical to clinical trials[11] and the quality and conversion of referrals[12,13].

Limitations

These findings should be interpreted within their methodological context. The sample size was modest and drawn from US sites with variable celiac disease research experience; some had conducted only a single celiac study, while others were more established. Self-selection bias, wherein sites that replied to the study invitation may be inherently more engaged, may have inadvertently excluded barriers felt by sites with more limited experience, success, or scheduling capacities. The authors acknowledge that only sites with experience utilizing the Celiac Disease Foundation's iQualifyCeliac™ platform qualified for inclusion, which may limit generalizability.

Data relied on retrospective, self-reported accounts from the site leadership perspective, which may underrepresent challenges or strategies felt differently by patients. This points to an additional need to assess barriers and facilitators to recruitment and retention from the patient perspective. Despite this, alignment of themes across principal investigators and coordinators, and their consistency with previously documented barriers in clinical research, strengthen the validity and transferability of these insights.

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Recommendations

To translate these findings into practice, sponsors and study sites should implement targeted strategies incorporated in the accompanying **Best Practices Toolkit for Celiac Disease Research**, emphasizing patient-centered communication, operational agility, and advocacy partnership integration. The authors acknowledge that differences in site organization, management, and study protocols may limit the adoption of certain toolkit components and recommend that researchers employ methods best suited to their specific resources and context.

With the support of the **Celiac Disease Foundation's Clinical Trial Site Advisory Council** (Addendum), we recommend that:

- **Sponsors** incorporate early patient and site input into protocol design to identify and minimize unnecessary burdens such as excessive number or length of visits, pre-randomization gluten challenges, or highly restrictive eligibility criteria
- **Sites** focus on building rapport and adopting structured outreach workflows ensuring rapid contact with referrals, diversified communication methods, and flexible scheduling to accommodate patient lifestyles
- **All stakeholders** engage trusted patient advocacy organizations to co-develop informational materials, streamline referral pathways, and strengthen patient trust through community-based recruitment efforts

Conclusion

Recruitment remains the principal challenge in celiac disease clinical trials; nevertheless, this study identified specific, actionable practices including rapid, persistent, and tailored outreach, and strategic use of patient advocacy networks, that can improve enrollment efficiency. Retention appears generally robust but is supported by clear expectation setting and sustained participant engagement.

The best practices toolkit derived from these findings offers a practical, adaptable resource to strengthen clinical trial efforts across a range of sites and may inform future initiatives aimed at accelerating therapeutic development in celiac disease.

Future investigations should aim to capture patient perspectives to build on the insights collected from site leaders, clarifying areas of alignment and revealing gaps that may inform more effective recruitment and retention strategies.

Acknowledgments

The authors would like to acknowledge Marissa Mahoney, Amanda Halligan, and Jackson Rau, of the Celiac Disease Foundation, for their contributions to data analysis.

Insights from the Clinical Trial Site Advisory Council

Following the completion of our study and subsequent account of its findings, the Clinical Trial Site Advisory Council (a group of global academic researchers, community principal investigators, and experienced clinical coordinators with expertise in conducting celiac disease clinical trials) reviewed this report and the resulting toolkit. Members contributed additional insights drawn from their collective experience across clinical, operational, and community-based research settings. The Council met in October of 2025 to discuss their feedback.

The Council reaffirmed the central importance of trust and communication in participant recruitment and retention, noting the importance of first contact with interested individuals and building a rapport with patients and their families. Members also emphasized the significance of enthusiasm and increased involvement on the part of the principal investigator. The Council similarly confirmed that reviewing medical records ahead of screening and standardizing educational materials to improve study activities, like the gluten challenge, could optimize study success. As expected, due to the mix of administrative frameworks and contextual factors, not all recommendations may be feasible for every site, therefore further emphasis was placed on the adaptability of the toolkit and variable implementation of strategies where possible.

Council members also brought up a few concepts that were either not present or not heavily discussed during the study's interviews. This included the importance of using both symptom-based *and* objective measures in inclusion criteria to optimize enrollment, given the diverse real-world manifestations of celiac disease (e.g., atrophy with few symptoms and vice versa) and overlap of symptoms among comorbidities. Council members also highlighted the opportunity for principal investigators to discuss recent events in celiac disease research with their patients (during regular clinic visits) to improve engagement and enthusiasm for new discoveries.

While this study already found that patients with celiac disease tended to be particularly interested in their health data and the results from testing, Council members noted that it was not always within budget or protocol to share findings or pursue further care if abnormalities were found during study procedures. This highlighted an area for potential collaboration between sponsors and clinicians to integrate patient-centered benefits in support of shared goals. Finally, it was also recommended that site teams emphasize to patients that their contribution and involvement is critical to the cause and necessary to see any progress in this space.

We thank the members of the Clinical Trial Site Advisory Council for their review and contributions. **Insights from this review directly informed revisions to the paper and toolkit, strengthening their alignment with best practices in participant engagement.** The Council's perspectives provide essential context and practical guidance that will continue to inform future strategy and program development.

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Best Practices Toolkit for Celiac Disease Research

Purpose

This toolkit translates qualitative findings from U.S. celiac disease clinical trial sites into actionable recommendations to improve patient recruitment and retention. It is intended for principal investigators, site coordinators, sponsors, and CROs conducting or planning celiac disease clinical trials.

Background

Recruitment and retention remain key challenges in celiac disease clinical trials, with patient concerns about gluten challenges and protocol expectations complicating enrollment.

Goal of Toolkit

Provide practical, evidence-informed strategies to accelerate enrollment, sustain retention, and strengthen operational readiness. Recognizing that one size does not fit all, the authors encourage teams to modify toolkit recommendations in ways that are both practical and meaningful for their setting.

How It Was Developed

Derived from semi-structured interviews with experienced investigators and coordinators at sites with celiac disease clinical trial experience. Reviewed and endorsed by the Celiac Disease Foundation's Clinical Trial Site Advisory Council.

Recruitment Best Practices

Leverage Patient Advocacy Partnerships

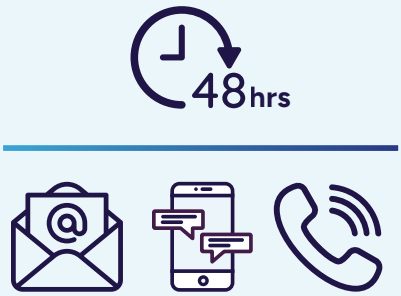
- Partner with organizations like the Celiac Disease Foundation to broaden reach, enhance trust, and increase enrollment

Multi-Channel, Tailored Outreach

- Use phone calls, text messaging, and email
- Adjust outreach to patient preference and age
- Consider sending a text ahead of a phone call so individuals can recognize the number
- Regularly conduct outreach outside of normal business hours to accommodate work/class schedules

Rapid & Persistent Outreach

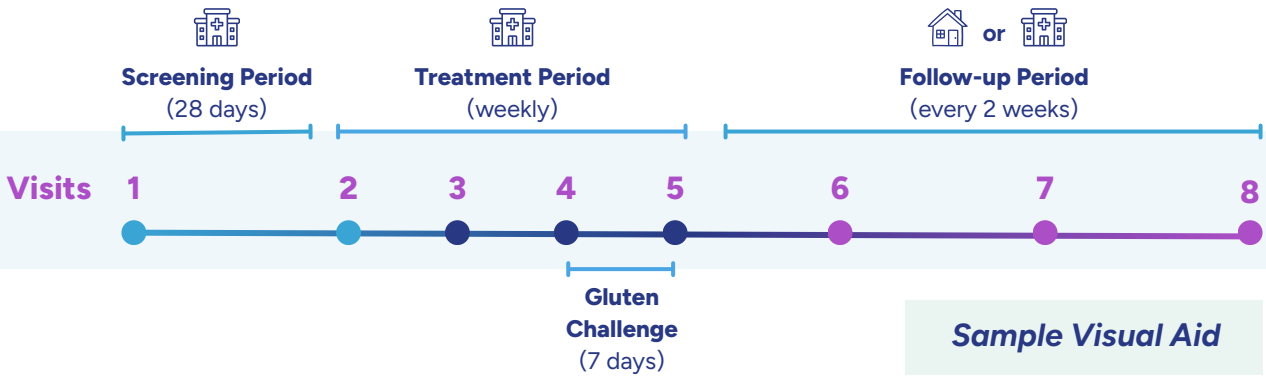
- Contact referrals within 24–48 hours; consider making more than three contact attempts before classifying as unreachable



Recruitment Best Practices (Continued)

Patient Preparation & Early Trust-Building

- Send informed consent forms ahead of first clinic visit
- Provide plain-language materials and visual aids when describing trial details
- Ensure principal investigator availability for one-on-one time with interested patients
- Spend time clarifying:
  - Rationale, medical supervision/safety, and controlled aspects of gluten challenges (as applicable)
  - FDA safety requirements (e.g., preclinical testing)
  - Opportunity to withdraw
  - Expectations regarding maintaining gluten-free diet



Sample Visual Aid

Trial Awareness & Marketing

- Ensure patients have easy access to clinical trial informational materials (e.g., utilize QR codes around waiting areas and clinic rooms)
- Reach out to colleagues and clinical networks for clinician referrals
- Provide materials to local businesses with gluten-free offerings
- Attend in-person community/educational events to spread clinical trial awareness

Operational Readiness

- Streamline medical record retrieval, consider sending a medical record release request ahead of screening
- Prioritize review of medical records ahead of a patient's first in-person visit
- Develop a deep understanding of eligibility criteria among staff
- Prioritize early referral review to frontload screening activities

Recruitment Best Practices (Continued)

Inclusion/Exclusion Criteria

- Protocols should clearly define exclusionary comorbidities which may confound trial findings
- Sponsors should take heterogeneous diagnosis practices into consideration when assigning the required medical records for inclusion
- Incorporate evidence-based and clinician informed objectives during protocol development

Patient Motivations

- Highlight that trial participation affords access to more health care than is standard

Retention Best Practices

Flexible & Participant-Friendly Scheduling

- Offer extended hours, weekend availability, and adaptable appointment times
- Utilize virtual or mobile visits in protocols where possible to be more accommodating

Ongoing Communication & Engagement

- Maintain regular, proactive contact and check-ins between visits, with an emphasis on well-being
- Provide direct staff access / contact information

Instill Confidence with Considerate & Supportive Care

- Build rapport
- Demonstrate an appreciation for patient contribution
- Provide results from clinic testing
- Offer 24/7 support
- Consider how presentation informs the patient perspective – ensure staff conduct is friendly, professional, and organized

Reduce Participant Burden

- Support travel logistics
- Arrange visit activities to increase efficiency and minimize unnecessary time at the site for patients and companions
- Tailor difficult procedures, like the gluten challenge, to individual preferences (e.g., water temperature or liquid used for slurries)

Retention Best Practices (Continued)

Set Clear Expectations from the Start

- Prepare participants for visit demands – communicate expectations for the trial journey and average visit durations early

Create a Positive Experience & Environment

- Provide private rooms, gluten-free snacks, and allow companions to attend visits

Encourage Transparency

- Suggest that patients have a conversation with the team if considering withdrawal

Implementation Tools

Sites may wish to develop or adapt the following materials to support implementation of these best practices:

- **Recruitment Workflow Checklist** – step-by-step guide from referral receipt to screening
- **Participant Education Materials** – adaptable for specific activities or clinical trial features that require more in-depth explanations (e.g., gluten challenge)
- **Study Overview Template** – visual aid and/or plain-language summary of study visits (including a breakdown of activities per visit) and overall study schedule

Key Takeaways

- Early and persistent engagement drives recruitment
- Operational readiness and advocacy partnerships multiply impact
- Clinically informed choices and well-defined processes during development lead to higher quality results
- Tailored communication and trust-building encourage engagement
- Patient comfort and flexibility are essential to retention