Leveraging Virtual Technology to Conduct Clinical Trials in Inflammatory Bowel Disease

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Abstract: Clinical trials have led to major advances in inflammatory bowel disease (IBD) care over the last few decades, yet in that time most clinical trial protocols in IBD have remained markedly the same. Many IBD protocols often still require face-to-face visits and monitoring, hospital-based medication administration, paper-based forms and questionnaires, and short follow-up periods resulting in limited long-term data. These factors have recently been recognized as likely contributors to the low recruitment and lack of diversity of participants across clinical trials in IBD. However, with increasing technological advances, there is now an opportunity for improvement. This article assesses a range of virtual innovations for how they may offer digital solutions to challenges currently encountered in IBD clinical trials. Such solutions include consideration for increasing patient diversity, digital invitation, remote consent and recruitment, virtual visits, remote patient monitoring and data collection, remote medication delivery and administration, remote clinical trial monitoring, and routinely collected health data for long-term follow-up. Adoption of virtual technology may drive the field toward patient centricity and more efficient trial protocols to allow for a new era in IBD clinical trials.

Keywords
Inflammatory bowel disease, clinical trials, digital, virtual, remote, patient centricity

Randomized controlled trials (RCTs) have been critical for generating data to support new advances in both Crohn's disease (CD) and ulcerative colitis (UC). In the last few decades, major advances have been made in the way clinical trials are conducted for CD[1] and UC.[2,3] However, investigators of modern-day clinical trials in inflammatory bowel disease (IBD) face many challenges, one of which is declining enrollment, widely referred to as a recruitment crisis.[4-6] The challenge with IBD clinical trial recruitment was magnified during the COVID-19 pandemic,[7] with the move toward virtual clinical care[8,9]

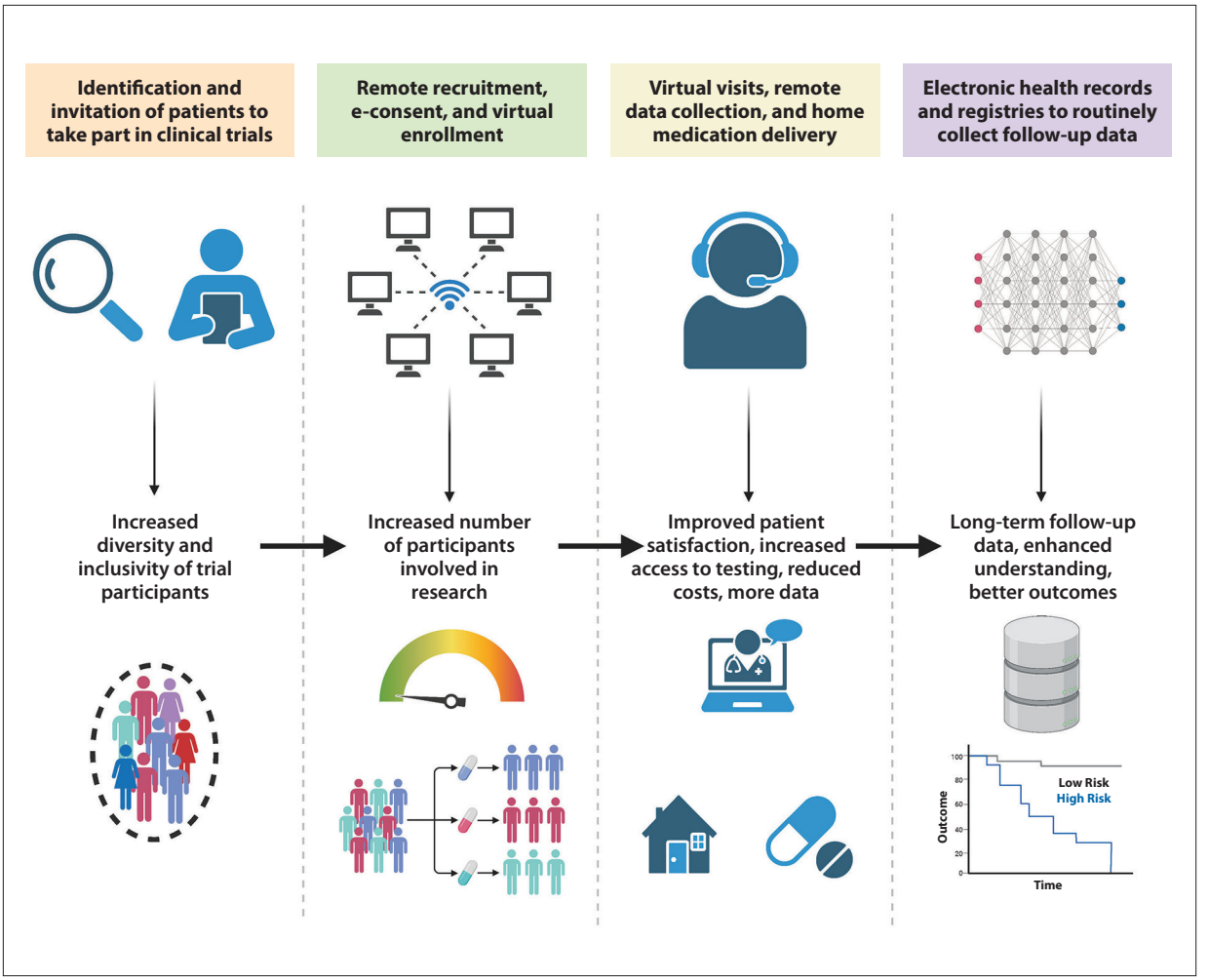

Figure. A digital road map for conducting clinical trials in inflammatory bowel disease, with recommendations for how to incorporate virtual technologies and the potential outcomes of digitization.

and virtual clinical trials.[10] One of several terms used to refer to this movement is the process of digitizing clinical trials.[11] Indeed, the COVID-19 pandemic demonstrated how increasingly digitized clinical trials could be conducted with success.[12] Given the successes seen in other disease areas, there now appears to be an opportunity for wider use of digitized clinical trials in the field of IBD,[13,14] with a focus on patient centricity (Figure).[15] This article examines a range of virtual innovations to address current challenges with clinical trials in IBD.

Consideration for Increasing Patient Diversity

As the number of registered clinical trials worldwide has risen exponentially[16] paralleled by the rise of clinical trials in IBD, the many challenges with conducting these trials have become apparent.[4,17,18] One of the major barriers to conducting clinical trials in IBD has been the extremely restrictive eligibility criteria, which have likely contributed to low recruitment rates.[19] Most historical trials in IBD have excluded patients with more severe phenotypes or subtypes of disease considered as harder to treat.[20-23] Studies of IBD clinical trials have reported a lack of inclusivity and diversity in patient characteristics such as age[23] and ethnicity.[24-26] Indeed, the historical requirements for face-to-face clinical visits and handwritten signatures for consent have likely contributed to the low levels of research involvement by patients from remote locations and ethnic minority groups.[27] This has resulted in the criticism that IBD clinical trials lack real-world applicability because patients enrolled have often not been representative of patients seen in the majority of clinical settings.[28] In addition to restricted inclusion, the desire to collect as

much data as possible, often through mandated face-to-face clinic visits, and with multiple and repeated invasive procedures such as endoscopy, has resulted in an entirely valid criticism about the lack of patient centricity in many IBD trial protocols.[15]

Digital Invitation to Increase Recruitment

Digital invitation was used successfully during the COVID-19 pandemic to help patients participate in clinical trials and overcome the challenge of low recruitment.[12] For many years, investigators in the field have queried whether it might be possible for trial invitations to be sent in a direct and focused manner to individuals who would be eligible or interested in taking part in a trial. Until recently, infrastructure and ethical/regulatory processes were not in place to make this a reality. The development and growth of large patient cohorts such as IBD Qorus in the United States[29] and IBD BioResource in the United Kingdom[30] offer significant potential for use of digital invitations. When patients sign up to a cohort, typically, they can indicate their willingness to be contacted about future clinical trial opportunities.

Automated invitations can be sent to large patient registries, biobanks, and other big data projects and can help identify patients who may meet eligibility criteria for trials.[31] For digital invitations to become more widely adopted in IBD, challenges need to be overcome, namely, how to ensure protection of data and privacy of individuals and, regarding recruitment, how to address the increasing mobility of patients. IBD care may transfer between sites or even be at multiple sites, with different services available to patients. This can pose challenges for trial investigators to identify and approach patients as well as for patients not knowing who they can approach for information about clinical trial involvement. Such scenarios emphasize the continued importance and need for local site investigators and research teams to conduct clinical trials and emphasize that digital trials would not make research teams redundant. A further and complementary digital process would be to offer patients the opportunity to actively seek out clinical trials that are available and for which the patients may be eligible. One digital system developed in France has generated considerable interest. The system uses geolocation of patients and crossmatches this against basic information patients enter into an electronic health care (e-health) app to determine whether there may be a clinical trial for which that individual patient would be eligible to take part in; the app also provides contact details of the trial team.[32] Such methods employing digital technology offer practical solutions to the challenges of low and declining recruitment in IBD clinical trials.

Remote Consent and Recruitment

A critical component of any interventional trial in IBD is the process of informed consent, usually resulting in a patient signing a consent form to indicate their willingness to be a trial participant, typically with either formal or more informal reaffirmation of consent at each trial visit.[33] Remote recruitment through use of telemedicine consultations and/or even more advanced technological solutions such as e-health apps, which allow patients to self-screen and enroll in a clinical trial without any contact with local site investigators, may help increase patient involvement in research. In addition, it is hypothesized that electronic consent (e-consent) may improve access to underrepresented minority groups.[34] This concept, which would have been anathema to many trial sponsors and regulators prior to the COVID-19 pandemic, is being used successfully in disease areas outside IBD.[35] However, with any solution requiring use of virtual technology, there are pitfalls, including the need for access to software or hardware, digital literacy, and familiarity with the technology. In addition, it is important to ensure appropriate account creation for patients who may have cognitive and/or any sensory deficits that would make virtual technology or remote recruitment challenging.

When remote recruitment is used, it is typically accompanied by the possibility for e-consent with electronic signatures (e-signatures) in addition to more traditional approaches. This variety of available options is a central tenet of building clinical trials around the needs and preferences of individual patients.[36] The process of consenting and whether e-consent would be desirable depends on multiple factors, such as the nature and complexity of the proposed research, including risks and burdens for participants, as well as any ethical issues arising from the research. For clinical trials involving high-risk interventions, it may remain that traditional face-to-face approaches would enable more lengthy and appropriately detailed discussions before deciding whether to proceed to clinical trial inclusion. Especially for patients with chronic disease such as IBD, the patient-clinician relationship is important and bidirectional, often developed over many years. A significant unknown is how remote recruitment and virtual health care may affect this patient-clinician relationship. It is possible that patients may find it harder to ask appropriate questions without the ease of face-to-face consultation. Another ongoing challenge of e-consent and e-signatures is regulatory oversight that may include requirements for the storage, security, audit, and inspection of data. In this regard, it is important that regulatory agencies be involved in facilitating movement toward remote consent processes in clinical trials.

Virtual Visits

Before the COVID-19 pandemic, telemedicine and virtual health were not a routine aspect of management in most health care settings around the world.[37,38] The pandemic acted as a key driver for widespread adoption of virtual health and telemedicine across routine IBD clinical care.[8,9] Even before the pandemic, a growing evidence base supported virtual health care and a desire from many patients for clinical practice to accommodate modern lifestyles and commitments (eg, work, study, childcare, holidays) and to appreciate the time and costs of repeated travel to and from hospital clinics.[39] Globally, the pandemic sparked a move toward virtual clinical trial consultations.[40,41] In many instances, trials maintained traditional approaches to recruitment and consent but allowed provision for virtual trial visits and remote data collection (sometimes called decentralized or hybrid virtual clinical trials).[12,42] An important area for future research will be to understand better the differences between face-to-face consultations and audiovisual or audio/telephone-only consultations. Going forward, virtual consultations will likely represent at least a portion of standard health care visits, and clinical trial protocols in IBD need to reflect day-to-day IBD clinical practice.[15] There may be additional benefits from virtual visits because fewer in-person visits require less travel, which could reduce the carbon footprint of clinical trials.[43]

Remote Patient Monitoring and Data Collection

Virtual health care and use of e-health apps have been associated with high levels of acceptance among patients, greater feelings of empowerment,[44] and reduced costs to health care providers[45] as well as patients through saved hospital visits and travel.[46] The interest in this topic remains high, with further ongoing projects such as the ASSIST study, which is exploring the utility of remote monitoring to assess medication adherence and persistence in IBD.[47] One of the key criticisms of using remotely collected data or self-reported data in apps is the lack of validation in the virtual health care setting. However, findings from studies evaluating patient-reported data are reassuring. For example, one study from Spain reported a high percentage of agreement between patient self-rated Harvey-Bradshaw Index scores in a mobile app and physician-rated scores in clinic.[48]

A related but distinct aspect of remote monitoring is the rise of technologies to enable self-administered procedures or assessments that historically were only provided in a clinical setting. A notable example is the electrocardiogram, which can be accurately recorded by an app routinely available on smartphones.[49] In addition, there is clinical validation that therapeutic drug monitoring can be achieved through dried blood samples collected by patients at home.[50] Perhaps the most widely used remote monitoring test in IBD to date is the home-based measurement of fecal calprotectin.[51,52]

With the rise of novel technologies such as home-based fecal calprotectin monitoring,[51,52] IBD-focused data apps,[53] and the ability to collect data from wearable devices,[54,55] a move toward entirely digital clinical trials is possible. Approaches that combine different sources of remotely collected data may even help reduce the need for repeated endoscopic procedures and hospital visits for future patients. Indeed, a combination of results from fecal calprotectin testing and a novel self-recorded patient outcome measure has been shown to accurately detect active inflammation.[56] However, in order to institute remote monitoring and digital data collection routinely, clinical trial investigators will need to overcome the operational burden of technology adoption and the time burden to verify data in a virtual clinical trial setting.[57] They will also need to appropriately convey monitoring results to patients and ensure that patients are able to communicate with health care practitioners about any areas of uncertainty or concerns regarding the results.

Remote Medication Delivery and Administration

With an appropriate and increasing focus on patient preferences has come increased understanding that many patients with IBD would prefer a medication they can self-administer at home or when traveling.[58,59] Although there remains enthusiasm for home-based infusions in some countries,[60] recent data raise questions about whether such infusions are optimal and cost-effective for patients.[61] Subcutaneous medications are widely used already for IBD in many countries, and oral therapies offer significant further promise for changing the method and mode of delivery for many patients with treatment in IBD. Delivery of subcutaneous or oral medications for IBD to patient homes is therefore an attractive and important aspect that can be considered to enable more efficient and more patient-oriented clinical trials. Indeed, examples of remote medication delivery being used in clinical trials already exist in the gastroenterology field. For instance, the UK trial RELIEVE IBS-D (ISRCTN17149988) was conducted in a fully virtual manner.[62] Patients in the trial consented virtually, received treatments delivered to their residence, and were able to input and provide data from the comfort of their own home. A similar ongoing trial in IBD utilizing the process of remote delivery of interventions, ADDapt (NCT04046913), is examining the role of

emulsifiers in mild-to-moderate CD.[63] It is important that trials with remotely delivered interventions have robust methods for patients to report adverse events.

Remote Clinical Trial Monitoring

Some aspects of clinical trials are antiquated owing to practices of trial sponsors or regulatory guidance. A notable example is the high level of on-site trial monitoring despite remote monitoring and virtual options being widely available. Data management and monitoring is a major aspect of IBD clinical trials that could be considered for digitization. During the COVID-19 pandemic, opening sites and conducting site-initiation visits routinely transferred to a virtual process.[10] Research has more recently recognized the efficiency benefits from remote and virtual data monitoring during ongoing conduct of a trial.[64] Increasing evidence has demonstrated no significant difference between remote monitoring and more traditional face-to-face visits in terms of both accuracy and completeness of data obtained.[48] Complete source data verification—a process that can take an inordinate amount of time and resources for both trial sponsors and recruiting sites, reducing the amount of time they can dedicate to patient care—can also be done remotely. With safety being one of the most important factors of any new therapy,[65] safety reporting can be a significant burden for both patients and site staff, typically resulting in underreporting in many clinical trials.[66] It is promising to note successful recent examples of self-reporting of adverse events by patients, which have helped to reduce administrative burden on sites conducting clinical trials and ensured more accurate reporting of adverse events.[67] Importantly, for instances of serious adverse events or nonserious adverse events that are still of particular concern to patients, there should remain mechanisms in place for patients to contact health care practitioners and have the possibility of clinical review.

Routinely Collected Health Data for Long-term Follow-up

Perhaps the greatest opportunity for digitization of clinical trials comes from wider and better use of electronic health record data.[11] It has become widely recognized that the concept of faster, better, and cheaper clinical trials is possible with routinely collected health data (RCHD). An aspiration in the field is for RCHD to be used to help obtain a clearer picture of longer-term outcomes following participation in a clinical trial. This is especially important for patients with IBD for whom long-term outcomes are most important. A vast majority of clinical trials in IBD have 1- or 2-year follow-up, with often short or minimal longer-term follow-up.[13,68] The reasons for limited longer-term data are numerous and include attrition of data, lack of funding, and clinical trial staff moving onto other projects over time. In this regard, RCHD offer a unique opportunity to help improve the value and impact of data obtained from RCTs. However, despite most trial teams reporting they would want to use RCHD for trial follow-up,[69] access to RCHD is difficult and successful applications to obtain access are reported to be very low.[70] Moreover, issues about data provenance (source of data) and data integrity (truthfulness of data) need to be addressed before RCHD can be widely used across clinical trials for follow-up.[71] Linking back to the importance of trial registries, it has been proposed that all major clinical trial programs should consider routine transfer or enrollment of patients into a subsequent disease registry to enable longer-term follow-up and key clinical questions to be answered for patients.[72] An additional point would be then for greater collaboration between academia and industry, with more widespread data sharing from trials,[73] to allow rapid translation of findings back to clinical settings.

Conclusion

In the last few decades, the process of conducting clinical trials in IBD has advanced, and clinical care has significantly changed over this time, with increasing remote and virtual care of patients. However, in that same period, failure to modernize clinical trial protocols in IBD has contributed to low recruitment and a lack of diversity of trial participants. With advances in virtual technologies, there is an opportunity to implement digitized clinical trials in IBD. Several recommendations for use of virtual technologies in clinical trials in IBD are outlined in this article, including digital invitations using large research patient registries and cohorts, virtual visits, remote consent and recruitment, digital data collection, remote delivery of medications to patient homes, and greater use of RCHD from trial participants over the long term. We believe these recommendations can serve as a digital road map that through collaborative efforts by trial regulators, funders, and sponsors working closely with clinicians and patients would considerably increase the quality, completeness, and speed of data collection in trials and potentially reduce the costs associated with conducting large clinical trials in IBD. Ultimately, adoption of digital solutions should result in increased participation of patients, greater diversity of participants, and more patient-centric clinical trials.

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