Despite efforts to enhance enrollment and the merger of national cooperative groups, <5% of patients with cancer will enroll into a clinical trial. Additionally, clinical trials are affected by a lack of diversity inclusive of minority patients, rural residents, or low-income individuals. COVID-19 further exacerbated known barriers of reduced physician-patient interaction, physician availability, trial activation and enrollment, financial resources, and capacity for conducting research. Based on the cumulative insight of academic and community clinical researchers, we have created a white paper identifying existing challenges in clinical trial conduct and have provided specific recommendations of sustainable modifications to improve efficiency in the activation and conduct of clinical trials with an overarching goal of providing improved access and care to our patients with cancer.
Electronic health record (EHR) order sets have been now incorporated into many practices to ensure that the oncology team can provide the recommended therapy in a safe, efficient, and uniform manner. Given its complexities, an EHR order set requires detailed preparation and extensive validation. ASCO discussed the importance of establishing formal treatment plan templates and/or summaries to foster communication between multidisciplinary providers and trial sponsors. The National Comprehensive Cancer Network has also recently collaborated with EPIC and Cerner PowerChart Oncology to provide templates, which would be especially helpful for providers with limited experience in developing EHR research protocol order sets. An EHR order set typically includes five basic components (Table 1). Figure 1 exemplifies the potential bottlenecks for the creation and validation of an EHR order set. A standard treatment template would reduce potential bottleneck delays in EHR order set development. The structure for these templates and specifics would vary based on the intricacy and phase of the trial. However, we believe that there are many ways to leverage existing information technology (IT) to design templates for all trials regardless of phase (ie, templates for dose escalation, templates for dose expansion, etc). Treatment templates could also be modified for subsequent protocol amendments.

**Recommendation**

The authors propose that all multi-institutional studies include standardized treatment order sets that are adaptable to different technology platforms as a means to communicate specific research treatment plans and to eliminate individual builds at each study site, thereby enhancing uniformity of care, workflow, patient safety, and reduced activation time while respecting flexibility for individual formularies.

**TELEMEDICINE OR TELEONCOLOGY**

Barriers to in-person contact during COVID-19 have significantly expanded the use of telemedicine in oncology, illustrating that necessity is the mother of invention. As concerns arose about virus transmission, teleoncology came to fruition. Defined as “the delivery of clinical oncology services via audio and video communication technologies to patients at a distance,” it has proven to be effective in providing remote consultations, treatment supervision, and palliative care. Regulatory restrictions have hampered widespread implementation of virtual visits.

Despite oncologists taking the same national board exams, various regulations exist regarding physician authorization across state lines and insurance reimbursement. To date, these regulatory impediments to telemedicine remain and vary state by state.

Discussion of a clinical trial can be overwhelming for a patient given the stringent guidelines of multiple visits at specified intervals, required laboratory tests, diagnostic imaging, and the investigational therapy to maintain the trial’s integrity and quality. Virtual tumor boards would provide an opportunity to bidirectional information and serve as a venue for referring providers and patients (community and academic). Virtual visits could also promote clinical trial education and awareness to underserved and rural patient populations. It is estimated that the median distance from patients’ homes to study sites is >25 miles, with disproportionately longer trips for lower-income and rural patients. The benefits of allowing virtual clinical trials are readily identifiable: increased accessibility, improved retention and compliance, and reduced cost, which have been established in standard of care for both cancer and noncancer conditions.

**TELEMEDICINE OR TELEONCOLOGY**

Clinical trial protocols should make allowances for telemedicine visits. Telemedicine visits can be used to review with patients’ current symptoms and medication changes and confirm adherence to prescribed medications. Keeping in mind that in-person visits may not necessarily replace face-to-face physician-patient interaction, virtual visits may vary per patient and protocol. Increasing virtual visits will require significant IT support for troubleshooting any technical issues. Patient familiarity and ownership of digital technology (eg, smartphones) are an important factor. A smartphone application (app) supported by the sponsor (eg, hospital, pharma, NCI, etc) would improve communication, provide real-time documentation, and reduce travel and patient and caregiver burden. The availability of telemedicine resources, and each patient’s ability to use telemedicine, can vary widely, however. It is imperative that this variability is considered carefully; otherwise, it can further increase disparity across cancer clinical trials.

**Recommendation**

Teleoncology offers an important means to increase access to clinical trials. Clinical trial participants should be offered the option of virtual visits, which would be defined in the study protocol.

**IDENTIFICATION OF TRIALS AND NEXT-GENERATION SEQUENCING**

Currently, there are general resources for accessing clinical trial information, including www.clinicaltrials.gov, but often these websites are difficult to navigate for patients and caregivers. Advocacy groups have initiated clinical trial identification to address this difficulty. Ultimately,
physician engagement is an essential determinant of clinical trial enrollment, and thus, there is a need for physician outreach to increase awareness. Next-generation sequencing (NGS) is considered routine for patients with metastatic cancer as the number of treatable molecular alterations has increased and the cost and turnaround time of NGS results have decreased. In 2017, > 75% of oncologists reported using NGS tests to guide treatment decisions to improve efficacy of therapy. Examples include tissue-agnostic FDA approvals of pembrolizumab for tumors with high microsatellite instability or high tumor mutational burden and detection of the BRAF mutation as an actionable mutation in melanoma and colorectal cancer, providing rationale for NGS for patients with metastatic cancers. In 2018, the Centers for Medicare & Medicaid Services determined National Coverage Determination for FDA-approved NGS companion diagnostic testing for patients with cancer. The NCI-Molecular Analysis for Therapy Choice provided a single platform for tumor genotyping and matching of patients to clinical trials (ClinicalTrials.gov identifier: NCT02465060). The prevalence of actionable mutations ranged from 1% to 7% with many molecular alterations occurring in < 3% of patients. The SWOG Lung-MAP study (ClinicalTrials.gov identifier: NCT03851445) is an example of a genotype-driven platform study that has enrolled > 2,000 patients into an umbrella protocol of multiple biomarker arms.

## TABLE 1. Common Components of an EHR Research Treatment Order Set Required for Institutional Validation

| Study Design Elements | Medication Elements | Administration Elements | Supportive Care Elements | Monitoring Elements |
|-----------------------|---------------------|-------------------------|--------------------------|---------------------|
| Number of treatment arms | Route of administration (eg, oral, intravenous, etc) | Line requirements | Antiemetic orders |
| Blinding and use of placebo | Frequency of administration | Dose rounding allowances | Vital sign requirements |
| Cycle length and days | Drug supply source | Calculated weight requirements | Laboratory requirements |
| Number of cycles | Allowance of biosimilar | Nursing communication orders | Biomarker and pharmacokinetic requirements |
| Infusion time appointments | Dose and modification guidelines | Administration times | Hypersensitivity orders |
|                       | Provider communication orders | Product-specific administration instructions (eg, vesicant, refrigerate, etc) | Discharge instructions |
|                       | Dilution and/or mixture requirements |                       | Procedure and/or diagnostic test requirements |

Abbreviations: EHR, electronic health record; PRN, Pro re nata or as needed.
The NGS results could be used to direct patients to specific clinical trials. Companies performing NGS have developed platforms and/or partnerships for genomic-driven clinical trials. Given the rarity of targetable alterations, it can be prohibitively expensive for most sites because of massive screening efforts, such as pancreatic cancer with a BRCA mutation and cholangiocarcinoma with FGFR2 fusions and rearrangements.45,46 For instance, for a biomarker-driven trial, a site may enroll a handful of patients, which is not cost-effective. Caris Life Sciences,47 Foundation Medicine,48 and Tempus49 use a master confidentiality research agreement. When a potential patient is identified, the physician is notified about the closest participating site. With further integration, physicians could be contacted by the NGS laboratory when their patients match. Foundation Medicine has partnered with Science37 to offer a virtual clinical trial platform where investigators connect with clinical trial patients, bypassing institutional study activation. In this decentralized model, brick and mortar sites are not required. Study visits are conducted by telemedicine, and an app is used for participants to remain connected to the study team.

Another approach would be to notify patients directly. Citizen is a consumer health company in partnership with The Cholangiocarcinoma Foundation, giving access to patients and enabling them to gather their medical records and NGS data and consolidate them into a profile sharable with their doctor, family, and researchers.50 Currently, none of the major NGS vendors send results directly to patients.

**Recommendation**

NGS platforms are widely used to guide treatment. Resources should be shared between NGS vendors, providers, and patients to help identify clinical trials and enhance enrollment.

**REMOTE CLINICAL TRIAL EDUCATION AND PRESCREENING**

Clinical trial enrollment is a multistep process. After initial discussion in the physician’s office, the patient is given the IC for consideration of the risks, benefits, and required pretreatment testing, which can be burdensome and a deterrent to enrollment.51,52 Telemedicine would allow this initial step to be conducted remotely. Additionally, opportunities to begin prescreening remotely by reviewing locally completed blood work, vital signs, and electrocardiograms would reduce delays and unnecessary travel especially for patients in remote areas. Obtaining consent via telemedicine can be used productively without compromising patient comprehension.53 Furthermore, the use of secured electronic signatures or smartphone apps that allow faxing or scanning could replace wet signature originals.

To encourage patients to participate in a trial, a partnership with a local oncologist or a hybrid and/or co-site enrollment model for phase II and/or III trials would be of immense benefit. The clinical research assistant (CRA) and/or research nurse would provide a copy of the protocol, study schema, and the study calendar to the local oncologist. The CRA and/or research nurse would follow up with all necessary labs, scans, and other required components of the clinical trial. Although the patient is under the care of their local oncologist, a telemedicine visit with the study site PI and/or collaborator conducted every 4-8 weeks may reduce the risk of protocol violations.

**Recommendation**

Partnership between advocacy groups, trial sponsors, and research teams using innovative strategies can expand clinical trial awareness and availability for patients with cancer and expedite accrual to studies.

**MODIFICATIONS OF TRIALS WITH ORAL AGENTS**

Following COVID-19, many centers had to rapidly establish new procedures for oncology clinical trials. For some studies, shipping oral study medications directly to patients was facilitated. Some trials lend themselves to being partially or exclusively conducted via telemedicine, thereby making shipping of oral study medications a tenable option.

To guarantee high-quality and reliable processes for delivery of oral investigational agents, clear and concise standard operating procedures (SOPs) are essential. The most obvious of these is to ensure that the integrity of the shipment is guaranteed. Establishing standards for overnight temperature-controlled shipping with tracking and temperature monitoring would be required. Telemedicine visits and direct shipment of drugs must involve compliance with state and federal regulations, which might be complicated when crossing state lines. For interstate shipping, state-specific regulatory requirements must be met. SOPs should include critical logistics: contact with the patient before shipment to ensure proper handling upon arrival, protocols for communication between patient and research staff for postdelivery confirmation of arrival and investigational agent integrity, telemedicine evaluation of the patient and review of instructions, short-term follow-up after starting the medication to confirm patient understanding and compliance, and prepaid return shipping materials for empty bottles and unused medication. These issues should be analyzed before implementation but would substantially ease the burden on patients with cancer.

**Recommendation**

Trials of oral cancer therapies could make greater use of telemedicine, and a framework for direct patient shipping of experimental therapeutics should be established.

**CAPTURE OF ADVERSE EVENTS OR PATIENT-REPORTED OUTCOMES**

It is now widely accepted that patient-reported outcomes (PROs) are important assessments that accurately capture a patient’s quality of life, adverse events, or other symptoms from their cancer.54-56 The US FDA defines a PRO as “any report of the status of a patient’s health condition that
comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.\textsuperscript{57} Data can include information about health-related quality of life, symptoms, function, satisfaction with care or symptoms, adherence to prescribed medications or other therapy, and perceived value of treatment.\textsuperscript{58}

Although PROs can be the primary or secondary end point of a study, they are often used to measure the adverse effects independent of effectiveness. There are several guidelines for how to incorporate PRO data into clinical trials.\textsuperscript{59}–\textsuperscript{61} The SPIRIT-PRO extension offers recommended items to include in clinical trials.\textsuperscript{62} The NCI PRO-CTCAE (Common Terminology Adverse Events) is a patient-reported outcomes version of the CTCAE that has been validated in large patient populations.\textsuperscript{63}

Capturing PROs via a smartphone or tablet app\textsuperscript{64} would be advantageous and would reduce recall bias. Other valuable data, including nutrition diaries and device information (eg, fitness tracker), could be captured providing valuable patient-generated health data (PGHD) information.

The PROs and PGHD data can be collected and used to help manage patient care. In one clinical trial, 766 patients were assigned to either standard care or a PRO, in which NCI-CTCAEs were self-reported by patients.\textsuperscript{65} If a PRO of concern was reported, the research nurse received an immediate e-mail alert. The primary end point, improvement of health-related quality of life at 6 months, was met, as well as an increase in overall survival by 5 months.\textsuperscript{66}

**Recommendation**

PROs are commonly integrated into clinical trials. A smartphone app would be advantageous in improved symptom management, expedited adverse event reporting, PGHD, and improved compliance.

**REGULATORY**

Site initiation visits (SIVs) are conducted before trial activation and are commonly conducted on-site where sponsor-assigned monitors review the protocol with the study team and inspect the facility to ensure that the site can successfully conduct the trial. Data suggest that on-site SIV may not make a difference in patient recruitment.\textsuperscript{57} In addition, SIVs are expensive, time-consuming, and difficult to coordinate because of scheduling conflicts. Remote SIVs could reduce cost, allow flexible scheduling, and reduce travel. Outside of the on-site facility inspection, a fair share of SIVs can be remote. Teleconferencing platforms can reduce the administrative burden on research sites and sponsors while still providing necessary training to all study team members.

Auditing of clinical trials is a critical component of ensuring high-quality research and data integrity and requires extensive resources. The traditional model includes in-person visits by nurses, pharmacists, physicians, etc, which are either at a priori set points (eg, enrollment of a certain number of patients and a preplanned interim analysis) or triggered by major protocol deviations and/or serious AEs.

These audits usually require site visits and reviews of all items related to the conduct of clinical trials: medical information, SOPs, delegation of authority logs, pharmacy and biological sample documentation, review board procedures, and physical infrastructure. Given advances in technology, most of this information can now be audited remotely. If most data queries and monitoring could be conducted remotely, this would reduce financial cost and time. Scaled over the entire clinical trial landscape, the time and resources saved by the sponsor and institutions could be beneficial. In addition, small, efficient web-based audits could be conducted more frequently, leading to earlier identification and resolution of problems.

**Recommendation**

The majority of SIVs and monitoring can be conducted remotely and should be incorporated into standard practice.

In conclusion, challenges in providing efficient and economically productive enrollment to clinical trials have been

| **TABLE 2.** Summary of Recommendations |
|------------------------------------------|
| **EHR order sets:** Standardized order sets of the study protocol treatments should be developed in adaptable technology platforms to eliminate the need for treatment builds at individual study sites |
| **Telemedicine:** Teleoncology offers an important means to increase clinical trial awareness and access. Clinical trial participants should be offered the option of virtual visits, and these may be defined in the study protocol |
| **NGS platforms:** Resources should be shared between NGS vendors, providers, and patients, to help identify clinical trials and enhance enrollment |
| **Education and accrual support:** Partnerships between advocacy groups, clinical trial sponsors, and research teams should be expanded to help expedite accrual to studies |
| **Oral therapies:** Trials of oral cancer therapies could make greater use of telemedicine, and a framework for direct-to-patient shipping of experimental therapeutics should be established |
| **Adverse event reporting:** Greater use should be made of technology solutions including smartphone apps to collect PROs, adverse events, PGHD data, and medication adherence information |
| **Regulatory:** Site initiation and monitoring can efficiently be done remotely and should be incorporated into standard practice |

Abbreviations: NGS, next-generation sequencing; PGHD, patient-generated health data.
emerging topics of discussion for years. Prolonged trial activation times, reduced patient participation, duplication of efforts, and subsequent costs are long-standing barriers associated with the successful conduct of clinical trials.68–71 As a consequence of the COVID-19 pandemic, many clinicians were forced to provide temporary innovative solutions to maintain the continuum of care for their patients. We propose expanding these temporary measures into enduring options to dismantle barriers to trial accrual while maintaining data integrity and preserving patient safety. Examples include standardizing treatment order sets; optimizing telemedicine to provide clinical trial awareness and education, as well as outreach to underserved patient populations; and the use of commonly available IT to allow for clinical trial matching based on molecular data (Table 2). Ideally, some of the financial resources could then be shifted to other resources needed for advances in cancer. Metrics and cost-benefit analyses would need to be supported to demonstrate benefit.

We strongly believe that these challenges can be overcome over time, with a focus on the common interest of providing improved access and care to our patients with cancer. We understand that these are not all the potential aspects of change required to improve the conduct of clinical trials, but we believe that these recommendations are feasible and transformative and can be accomplished with the support of all stakeholders: patients, patient advocates, healthcare providers, research organizations, the pharmaceutical industry, NCI, and the FDA.

AFFILIATIONS
1Vanderbilt-Ingram Cancer Center, Nashville, TN
2Division of Hematology and Oncology, Oregon Health and Science University, Knight Cancer Institute, Portland, OR
3University of Texas MD Anderson Cancer Center Pharmacy Clinical Programs, Houston, TX
4Intermountain Healthcare, Salt Lake, UT
5Moffitt Cancer Center, Tampa, FL
6Cleveland Clinic Taussig Cancer Center, Cleveland, OH
7New York University Langone Health, New York, NY
8Winthrop P. Rockefeller Cancer Institute, University of Arkansas, Little Rock, AR
9Kaiser Permanente, Los Angeles Cancer Clinic, Los Angeles, CA
10Moores Cancer Center, UC San Diego Health, La Jolla, CA
11University of Cincinnati Health Barrett Cancer Center, Cincinnati, OH
12Karmanos Cancer Center, Detroit, MI
13University of Texas MD Anderson Cancer Center, Houston, TX
14Virginia Mason Cancer Center, Seattle, WA
15Smilow Cancer Center, Yale School of Medicine, New Haven, CT

CORRESPONDING AUTHOR
Cathy Eng, MD, Vanderbilt-Ingram Cancer Center, Gastrointestinal Cancer Research Program, 2220 Pierce Avenue, 777 Preston Research Building, Nashville, TN 37232; e-mail: cathy.eng@vumc.org.

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AUTHOR CONTRIBUTIONS
Conception and design: Cathy Eng, Jane Rogers, Paul Oberstein, Mark Lewis, Smitha Krishnamurthi, Gary Buchschner, Emerson Chen, Stacey Stein
Administrative support: Cathy Eng, Emerson Chen, Gary Buchschner
Provision of study materials or patients:Cathy Eng, Emerson Y. Chen, Jane Rogers, Ramya Thota, Smitha Krishnamurthi, Paul Oberstein, Rang Govindarajan, Gary Buchschner, Sandip Patel, Davendra Sohal, Taymeyah Al-Toubah, Arvind Dasari, Hagan Kennecke, Stacey Stein
Collection and assembly of data: Cathy Eng, Emerson Y. Chen, Jane Rogers, Ramya Thota, Smitha Krishnamurthi, Paul Oberstein, Rang Govindarajan, Gary Buchschner, Sandip Patel, Davendra Sohal, Taymeyah Al-Toubah, Arvind Dasari, Hagan Kennecke, Stacey Stein
Data analysis and interpretation: Cathy Eng, Emerson Y. Chen, Jane Rogers, Mark Lewis, Jonathan Strosberg, Smitha Krishnamurthi, Rang Govindarajan, Gary Buchschner, Sandip Patel, Davendra Sohal, Taymeyah Al-Toubah, Philip Philip, Arvind Dasari, Hagan Kennecke, Stacey Stein
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Moving Beyond the Momentum: Innovative Approaches to Clinical Trial Implementation

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Cathy Eng  
Consulting or Advisory Role: Bayer Schering Pharma, Foundation Medicine, Array BioPharma, Natera

Emerson Y. Chen  
Other Relationship: Horizon CME, Taiho Pharmaceutical

Mark Lewis  
Consulting or Advisory Role: Boehringer Ingelheim  
Other Relationship: Medscape

Jonathan Strosberg  
Consulting or Advisory Role: Novartis  
Research Funding: Novartis

Ramya Thota  
Consulting or Advisory Role: Array BioPharma  
Research Funding: Abbvie, Bristol-Myers Squibb

Paul Oberstein  
Consulting or Advisory Role: Merck, BTG, Tyme, Ipsen  
Research Funding: Merck, Roche/Genentech  
Travel, Accommodations, Expenses: Merck

Gary Buchschacher  
Research Funding: Roche/Genentech, AstraZeneca, Merck  
Travel, Accommodations, Expenses: Roche/Genentech, AstraZeneca

Sandip Patel  
Consulting or Advisory Role: Bristol-Myers Squibb, AstraZeneca/MedImmune, Nektar, Compugen, Illumina  
Speakers’ Bureau: Merck, Boehringer Ingelheim  
Research Funding: Bristol-Myers Squibb, Pfizer, Roche/Genentech, Amgen, AstraZeneca/MedImmune, Fate Therapeutics, Merck

Davendra Sohal  
Consulting or Advisory Role: Perthera, Ability Pharma  
Speakers’ Bureau: Incyte  
Research Funding: Celgene, Genentech, Bristol-Myers Squibb, Rafael Pharmaceuticals, Apexigen, Amgen

Philip Philip  
Honoraria: Celgene, Bayer, Ipsen, Merck, AstraZeneca, TriSalus Life Sciences, Blueprint Medicines, Syncore, Array BioPharma  
Consulting or Advisory Role: Celgene, Ipsen, Merck, TriSalus Life Sciences, Daiichi Sankyo, Syncore, Taiho Pharmaceutical

Speakers’ Bureau: Celgene, Bayer, Ipsen, Novartis, Incyte  
Research Funding: Bayer, Incyte, Karyopharm Therapeutics, Merck, Taiho Pharmaceutical, Momenta Pharmaceuticals, Novartis, Plexikon, Immunomedics, Regeneron, Genentech, Tyme, Caris Life Sciences, ASLAN Pharmaceuticals, QED Therapeutics, Halozyme, Boston Biomedical, Advanced Accelerator Applications, Lilly, Merus, QED Therapeutics, Incyte, Caris Life Sciences

Travel, Accommodations, Expenses: Rafael Pharmaceuticals, Celgene, AbbVie

Arvind Dasari  
Consulting or Advisory Role: Ipsen, Novartis, Voluntis, Lexicon  
Research Funding: Novartis, Eisai, Hutchison MediPharma, Merck, Guardant Health, Ipsen

Hagan Kennecke  
Honoraria: Ipsen  
Research Funding: Taiho Pharmaceutical

Stacey Stein  
Consulting or Advisory Role: Genentech/Roche, Eisai, QED Therapeutics, Exelixis

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