September 5, 2023

The Honorable Robert M. Califf, MD, MACC
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

SUBMITTED ELECTRONICALLY VIA http://www.regulations.gov

Re: E6(R3) Guideline for Good Clinical Practice; International Council for Harmonisation; Draft Guidance for Industry; Availability (Docket No. FDA-2023-D-1955)

Dear Dr. Califf,

The Society of Gynecologic Oncology (SGO) and The GOG Foundation, Inc. (GOG-F) appreciates the opportunity to provide comments on the draft guidance titled "E6(R3) Guideline for Good Clinical Practice," prepared under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). SGO and GOG-F are encouraged to see significant updates to modernize clinical trial design from previous versions of this guidance. The revisions are consistent with technological advancements, ensure participant involvement, and promote the safety and the reliability of trial results.

The SGO is the premier medical specialty society for health care professionals trained in the comprehensive management of gynecologic cancers. Our 2,800 members, who include physicians, nurses, and advanced practice providers, represent the oncology team dedicated to the treatment and care of these patients. The society's purpose is to improve care by encouraging research and disseminating knowledge, raising the standards of practice in the prevention and treatment of gynecologic malignancies, and collaborating with other organizations interested in patient care, oncology, and related fields.

The GOG Foundation, Inc. is a not-for-profit organization with the purpose of promoting excellence in the quality and integrity of clinical and translational scientific research in the field of gynecologic malignancies. The GOG Foundation is committed to maintaining the highest standards in clinical trials development, execution, analysis, and distribution of results. The GOG Foundation is the only clinical trialist group in the United States that focuses its research on patients with pelvic malignancies, such as cancer of the ovary (including surface peritoneal malignancies), uterus (including endometrium, soft tissue sarcoma, and gestational trophoblastic neoplasia), cervix, and vulva.

The GOG Foundation is multi-disciplinary in its approach to clinical trials, and includes gynecologic oncologists, medical oncologists, pathologists, radiation oncologists, oncology nurses, biostatisticians (including those with expertise in bioinformatics), basic scientists, quality of life experts, data managers, and administrative personnel.

We appreciate your consideration of the following comments.

Principles of ICH Good Clinical Practice

Incorporation of Digital Health Technologies

The FDA has recognized that innovative digital health technologies, such as wearables and sensors, have the potential to expand clinical trial protocols in this draft guidance. SGO and GOG-F appreciate this recognition and agree that the incorporation of technological advancements will aid in keeping clinical trial conduct in line with advancing science and technological developments.

Digital health technologies are revolutionizing the way we gather patient-reported outcomes (PROs) and other patient data in clinical trials. While traditional PRO methods offer valuable insight, these data have fallen short in capturing certain aspects such as sleep efficiency, mobility, heart rate variation and other vital signs, stress, and other facets of fitness that are important to understanding treatment effects. While wearables allow for continuous monitoring and a wealth of real-time data, there are still gaps in the information they collect. To bridge these gaps, technologies such as ingestibles and injectables hold significant potential to capture biological functions and provide more significant data on the effects of treatment. Nonetheless, integration into regulatory strategies is dependent on FDA validation and regulatory approval. Clear guidance on how such devices and technology can be successfully integrated into clinical trial design and regulatory endpoints will foster innovation, broadening applications for use outside of the carefully constructed clinical trial environment.

The incorporation of digital health technologies must account for factors such as the digital literacy of individuals of diverse cultures and socioeconomic backgrounds. Additionally, challenges related to individual patients and social determinants of health (SDOH) must be considered in trial design, particularly broadband access. Specifically, technologies centered around web access should be affordable, designed to provide meaningful engagement for patients with a range of health literacy, and offer language support for populations beyond English and Spanish. It is essential to design clinical trials that not only take advantage of evolving technologies but also ensure inclusivity, equity, and meaningful engagement across diverse populations.

Diversifying Clinical Trials

SGO and GOG-F are pleased that the FDA recognizes the use of innovative clinical trial designs and technologies may help include diverse patient populations and encourage wider participation. Additionally, we agree that incorporating patients' perspectives may improve

quality and lead to more meaningful clinical trial outcomes. SGO and GOG-F strongly recommend that the FDA continue to encourage patient engagement in the entire clinical trial process, especially in trial design. To ensure that the patient voice is incorporated and there is broad patient engagement in trial design, we recommend there be more community advisory boards and greater inclusion of patient advocates and representatives from patient advocacy groups. The patient perspective should be a key component of any clinical trial design.

Moreover, initiative-taking engagement with trusted community influencers who understand the lived experiences of the population, particularly among underserved and minoritized populations, is equally important. Clinical trials must acknowledge the potential for lack of trust in institutions, medical research, historical injustices, and other factors that may contribute to reluctance towards engagement in such trials. The utilization of Patient and Family Advisory Councils and collaborative initiatives, like café series involving patients and partners focused on SDOH, is crucial for incorporating diverse perspectives into trial design. Clear provisions addressing potential barriers like transportation are vital to attracting diverse patient populations. Community outreach (i.e., places of worship, barber shops, hair salons) is paramount as is tailoring patient involvement to various trial endpoints to prevent imposing unnecessary burdens on a community. This approach respects patients' access to their community oncologists while navigating the complexities of launching trials within community settings, ensuring access to both care and clinical trial opportunities. We refer the agency to a recently published joint document from SGO and GOG-F highlighting barriers to and solutions for clinical trial access.[1] Moreover, it is equally important to foster diversity within research teams and the need for these teams to be aware of and address implicit biases to ensure more equitable, rigorous, and unbiased research.

Trial Design

Adaptive designs and the incorporation of synthetic controls for comparison are innovative approaches to enhance the efficiency, flexibility, and accuracy of clinical trials. The requirement to enroll additional participants when they represent populations with known response rates might seem excessive; however, with an innovative trial design we can overcome this inefficiency and enroll fewer participants while leveraging prior knowledge of response rates from external controls. Incorporating innovative trial designs is particularly important when pursuing avenues like breakthrough designation and accelerated approval and could be referenced as a sensitivity analysis against real-word interventions for regular approval applications – particularly to improve diversity and address other SDOH. Additionally, incorporating feedback loops and triggers into the trial design to continuously monitor participant accrual rates in real-time is vital. It is also important to note that the timeline for securing approval may vary between pharmaceuticals. This variability emphasizes the need for flexible and adaptive trial designs that cater to the unique characteristics of clinical trials.

[1] Pothuri,et al,. Gynecol Oncol 2023; 174:278-287

Furthermore, the process of biomarker development would benefit from innovative trial design. Currently, there is inconsistent guidance regarding biomarker development particularly regarding classification of a biomarker as a companion diagnostic or a complimentary diagnostic. Improving statistical methodology and fostering innovative trial designs would undoubtedly accelerate biomarker development and lead to improved patient outcomes.

Informed Consent of Trial Participants

SGO and GOG-F believe that informed consent policies in clinical trials should be implemented in a way that benefits the patient and reduces burden for the patient and provider. Technological advances and lessons learned from the COVID-19 pandemic, like remote/video consent and phone consent options should be incorporated into trial design to respond to evolving risk profiles when consenting patients. The implementation of remote consent not only streamlines the consenting process but also reduces patient burden and enhances accessibility and efficiency of clinical trials.[2,3] The integration of telehealth for safety follow-up is crucial as patients are often not able to travel for these visits. Telehealth and broadband access are also critical to enable continued participation in clinical trials. Institutions and providers have demonstrated the capacity to successfully deploy telehealth and obtain remote consent for a range of clinical trial treatments, like chemotherapy. These policies should be made permanent to ensure that patient-centricity, accessibility, and technological innovation remain at the core of informed consent policies since they have demonstrated their value during the pandemic. Additionally, SGO and GOG-F recommend that the FDA support the implementation of translated consent forms to help improve enrollment for non-English speaking patients. This will help improve access to clinical trials and diversification of trial enrollees.

Quality Management

SGO and GOG-F agree with the draft guidance recommending that sponsors implement an appropriate system to manage quality throughout all stages of the trial process. Sponsors should identify risks that may have a meaningful impact on quality factors and risks should be considered across all aspects of clinical trials, especially the informed consent process. This principle is typically communicated in consent forms, acknowledging that while a trial might not directly benefit the participant, it could contribute to societal advancements. This is especially important for early-phase trials where there are many uncertainties. Ensuring informed consent involves a transparent discussion of risks and benefits is vital. SGO and GOG-F believe that Institutional Review Boards (IRBs) nationwide, in general, have maintained a balance between participant autonomy and ethical considerations.

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[2] Welch BM et al. Teleconsent: a novel approach to obtain informed consent for research. Contemp Clin Trials Comm 2016; 15(3): 74-79.

[3] Eng C et al. Moving beyond the momentum: innovative approaches to clinical trial implementation: JCO Oncol Pract 2021: 17(10): 607-614.

Sponsor Oversight
SGO and GOG-F appreciate that the updated "sponsor" section clarifies their responsibilities in trial design and execution. We believe that sponsors should strive to enhance the accessibility and affordability of trials for patients, particularly when it comes to pragmatic trials. There is a need for improved communication between the National Cancer Institute (NCI) and the FDA so that we can achieve an approach to clinical trial design that benefits patients, society, and supports drug development costs. Sponsors are not simplifying studies; however, NCI is suggesting that there are ways to reduce participant burden like fewer tests, follow-ups (remote/virtual, when appropriate), and less restrictive eligibility criteria. This is a discrepancy that should be resolved in guidance by encouraging better alignment between entities, like the NCI and trial sponsors.

Lastly, success of clinical trials requires actionable and accountable collaboration among patients, research teams, institutions, communities, and sponsors. This collaborative effort is underpinned by the development and publication of transparent accountability structures, ensuring that responsibilities and expectations are clear to all stakeholders. Embracing the culture of 'Just Ask' further reinforces this approach, promoting open communication, questions, and feedback, enhancing trial integrity, participant safety, transparency, and the generation of high-quality, reliable data.

Thank you again for the opportunity to provide these comments. Should you have any questions, please contact Katie Martino, Manger, Governance and Clinical Practice of SGO katie.martino@sgo.org and Jenna Cummins, Executive Director, Business Development at the GOG-F at jcummins@gog.org.

Sincerely,

Angeles Alvarez Secord, MD, MHSc
SGO President, 2023-2024

Thomas Herzog, MD
GOG President