Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Heather Stone, 301-796-2274, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2024
Real World Data/Real World Evidence (RWD/RWE)

Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice

Guidance for Industry

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

As part of FDA's Real-World Evidence (RWE) Program,[2] this guidance is intended to support the conduct of randomized controlled drug[3] trials (RCTs) with streamlined protocols and procedures that focus on essential data collection, allowing integration of research into routine clinical practice. Such trials have sometimes been referred to as *point of care trials* or *large simple trials*. Like decentralized clinical trials,[4] which aim to bring trial-related activities to patients' homes or other convenient locations, such RCTs may improve convenience and accessibility for participants and allow for enrollment of more representative populations, resulting in more generalizable trial results. Leveraging established health care institutions and existing clinical expertise in the medical community can reduce startup times and speed up enrollment.

Depending on the condition and the intervention to be studied, the spectrum of trial designs may range from those that are almost completely reliant on data acquired by the participant's local health care providers (HCPs) during routine clinical practice visits (either in person or virtually)

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Oncology Center of Excellence at the Food and Drug Administration.

[2] The 21st Century Cures Act (Cures Act) aims to accelerate medical product development and bring innovations faster and more efficiently to the people who need them most by capitalizing, among other things, on the use of RWE. In response to the Cures Act, which added section 505F to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355g), relating to the use of RWE in regulatory decision-making, the FDA created an RWE Program to evaluate the use of RWE to support the approval of new indications for drugs already approved under section 505(c) of the FD&C Act (21 U.S.C. 355(c)) or to help to support or satisfy postapproval study requirements. The RWE Program also covers biological products licensed under section 351(a) of the Public Health Service Act.

[3] The term *drug* in this guidance refers to both human drugs and biological products unless otherwise specified.

[4] See the guidance for industry, investigators, and other stakeholders *Conducting Clinical Trials With Decentralized Elements* (September 2024). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

to those that require significant supplementation with dedicated, research-specific activities for data collection conducted by trial staff. The contribution of local HCPs involved in clinical care and the contribution of dedicated trial staff may also vary, depending on the needs of the trial.

During routine clinical practice visits, local HCPs are often engaged by organizations to perform clinical activities that are not required as part of routine clinical care, such as insurance or employment medical examinations, medical examinations for drivers' licenses, or medical examinations for visa applications for travelers. Examples of activities local HCPs can conduct for these organizations include obtaining a medical history, conducting a physical examination, and performing a diagnostic procedure. These activities do not require that practitioners receive special training beyond their specialties or that they have a detailed knowledge of why the information is being requested. If practitioners find an abnormality during these activities, they typically record the finding and ensure appropriate clinical management (e.g., referring the participant back to their own local HCP if they are not the patient's HCP).

In a similar fashion, sponsors may engage local HCPs (either directly or through clinical investigators or health care institutions) to perform certain clinical activities that are not required as part of routine clinical care but might be needed for the purposes of a clinical trial, such as conducting a routine physical examination, ordering a chest radiograph, ordering a blood test at protocol-specified intervals, or collecting protocol-required information such as medical histories or outcomes. Sponsors should consider the complexity of trial requirements, the need for standardization of trial-related activities, and the need for research-specific expertise when deciding on the feasibility of trials in a practice setting. The integration of RCTs into clinical practice should not interfere with the appropriate delivery or administration of patient care.

In this guidance, the terms *investigator* and *subinvestigator* will be used for individuals who meet the definitions for those roles under 21 CFR 312.3.[5] The use of the term *local HCPs* will be restricted to health care providers who are involved in the trial but based on the limited tasks they perform are not serving as trial personnel (i.e., investigators, subinvestigators, or their clinical support staff) (see section V.A.3).

As with traditional trials (i.e., those with only dedicated trial staff and sites), RCTs that are integrated into clinical practice may also seek to use real-world data that are available from electronic or other health records to inform safety or effectiveness, without the direct engagement of local HCPs. Examples of such data include demographic information, pharmacy data on prescriptions, diagnostic codes, and discharge summaries. The use of these data is covered in the guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* (July 2024).

This guidance applies to studies involving FDA-approved drugs being studied for new indications, populations, routes of administration, or doses; drug safety studies for FDA-

[5] Under 21 CFR 312.3, an investigator "means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 'Subinvestigator' includes any other individual member of that team."

approved drugs; other postmarketing studies for FDA-approved drugs; comparative effectiveness studies for FDA-approved drugs; and trials of unapproved drugs when the safety profile is sufficiently characterized and the drug is appropriate to be administered and managed in the setting of routine clinical practice (see section IV.C.2). This guidance does not address non-interventional (observational) studies.

Sponsors are encouraged to employ a quality by design (QbD) approach (see section IV) to achieve the scientific objective and ensure adherence to FDA requirements, including those related to good clinical practice in FDA regulations.[6] Regulatory requirements for trials integrated into routine clinical practice are the same as those for traditional clinical trials.[7]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Traditional RCTs typically capture a large amount of protocol-specified patient information (e.g., patient characteristics, medical history, concomitant medications, vital signs, adverse events, laboratory results, measures of drug response, clinical status) at baseline and over the course of the trial. Some of these data are also collected in routine clinical practice, although the specific procedures and methods, timing of collection, and documentation formats often differ from those in a clinical trial. Given the potential overlap in information collected, data for clinical research can, under appropriate circumstances, be obtained from routine clinical practice interactions, reducing the need for dedicated trial sites.

There has been increasing interest in the use of real-world data acquired during routine clinical practice to support drug development. Advances in information technology and widespread use of electronic health records (EHRs) have facilitated access to real-world data obtained during routine clinical care and provided new opportunities for the integration of clinical research and clinical care. Institutions may be able to enhance the integration of clinical research and clinical care by designing EHR systems that capture health care information in standardized formats aligned with the format of information collected in case report forms used in RCTs.

Experience with trials conducted in clinical practice settings has demonstrated the potential value of this approach for drug development in certain circumstances. Such trials with simplified data

[6] See the web page Regulations: Good Clinical Practice and Clinical Trials, available at https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials, for a resource providing links to certain FDA regulations related to good clinical practice.

[7] Ibid.

collection have allowed for rapid enrollment and evidence generation.[8] Efforts to integrate clinical trials into routine clinical practice have been ongoing for many years. For example, in a trial conducted in the 1980s, coronary care units throughout Italy were used to investigate the benefits of streptokinase in the treatment of acute myocardial infarction, without the need for dedicated research sites.[9] More recently, the widespread use of EHRs and other electronic data-gathering tools has made integration of clinical research and care more feasible. As an example, in 2020, the RECOVERY trial was conducted using clinical practice infrastructure and local HCPs in hospitals throughout the United Kingdom. The results of the trial supported FDA approval of tocilizumab for treatment of hospitalized adult patients with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.[10,11]

III. DISCUSSION

A. Role of Sponsors, Health Care Institutions, Clinical Investigators, and Local Health Care Providers in RCTs Integrated Into Clinical Practice

1. Role of Sponsors in Engaging Health Care Institutions

Sponsors can engage health care institutions in clinical trials that are integrated into clinical practice. This approach may facilitate the enrollment of sizable trial populations in a short period of time by improving convenience and accessibility for participants.

Health maintenance organizations, hospital systems, clinical networks of HCPs, and national health systems in some other countries have played major roles in recruiting and engaging participants for clinical trials and providing an operational framework for trial conduct. The use of EHR systems to capture data for clinical trials integrated into clinical practice may also facilitate the participation of small community health care facilities that have historically been involved less frequently in FDA-regulated clinical trials. Sponsors might consider providing additional resources to participating health care institutions, such as service providers or contract research organizations, to manage specific research requirements.

Agreements between sponsors and health care institutions should document the responsibilities that are assumed by the institutions and their employees and the tasks that they will perform as part of the clinical trial. As appropriate, sponsors should also obtain agreements from local

[8] Eapen ZJ, MS Lauer, and RJ Temple, 2014, The Imperative of Overcoming Barriers to the Conduct of Large, Simple Trials, JAMA, 311(14):1397–1398.

[9] Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI), 1986, Effectiveness of Intravenous Thrombolytic Treatment in Acute Myocardial Infarction, Lancet, 1(8478):397–402.

[10] RECOVERY Collaborative Group, 2021, Tocilizumab in Patients Admitted to Hospital With COVID-19 (RECOVERY): A Randomised, Controlled, Open-Label, Platform Trial, Lancet, 397(10285):1637–1645.

[11] Actemra (tocilizumab): Highlights of Prescribing Information, revised October 2023, www.accessdata.fda.gov/drugsatfda_docs/label/2022/125472s049lbl.pdf.

HCPs to perform these protocol-related tasks, either directly or through the health care institutions in which they work.

Sponsors should ensure that the institutions and individual local HCPs they engage are suitably credentialed and qualified to participate in the research.

2. Role of Clinical Investigators

Clinical investigators can be affiliated with the institutions or health care systems where trials are conducted. Clinical investigators external to these institutions can also be engaged by sponsors. Clinical investigators' responsibilities for supervising the conduct of the trial are the same whether they are affiliated with the local health care system or not.[12]

Clinical investigators are responsible for ensuring that a trial is conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and for protecting the rights, safety, and welfare of participants in the trial, as required under 21 CFR part 312.[13] These responsibilities are also discussed in Form FDA 1572 and various guidance documents, including the guidance for industry *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects* (October 2009).[14] Form FDA 1572 must be completed by clinical investigators and include their names, their addresses, and the names and addresses of any medical school, hospital, or other research facility where the investigation will be conducted.[15]

Investigators should enroll only as many trial participants as they can appropriately manage and must ensure adequate supervision of trial-related activities, including adequate supervision of those to whom they have delegated these activities.[16] Clinical investigators must review pertinent trial-related records provided by local HCPs[17] and must ensure the accuracy and completeness of data that are needed to meet trial objectives and ensure patient safety.[18]

Some trials may involve procedures that contribute directly and significantly to trial data and require study-specific training or detailed knowledge of the protocol. Although these procedures may be performed by clinicians working as part of a health care institution engaged by the

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[12] See 21 CFR 312.60.

[13] Ibid.

[14] See also the International Council for Harmonisation (ICH) draft guidance for industry *E6(R3) Good Clinical Practice* (May 2023). When final, this guidance will represent FDA's current thinking on this topic.

[15] See 21 CFR 312.52(c)(1). See also sections 1 and 3 of Form FDA 1572. Clinical practice sites should be listed in section 3.

[16] See 21 CFR 312.60. See also the guidance for industry *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects*.

[17] See 21 CFR 312.62.

[18] See 21 CFR 312.60 and 312.62.

sponsor or in independent practices, unlike local HCPs, these individuals would be considered either investigators or subinvestigators or other trial personnel depending on their roles in conducting the trial.[19]

Procedures or processes that contribute directly and significantly to trial data[20] should be conducted by trial personnel. Such activities include:

- Determining whether a trial candidate satisfies the trial's enrollment criteria
- Conducting specialized assessments required by the protocol that are not part of routine clinical care and require trial-specific training and expertise (e.g., evaluating tumor responses using RECIST guidelines)
- Assessing whether a trial-related adverse event is attributable to the investigational product
- Applying protocol-specified criteria for dose modification or discontinuation of investigational products
- Determining that a trial participant has reached a trial endpoint

3. Role of Local Health Care Providers

Local HCPs working as part of health care institutions or individual practices may be engaged to perform tasks that do not require trial-specific knowledge, trial-specific training, or research expertise, although they might need limited instructions to ensure that these tasks are performed as required. These tasks should not differ from those that they are qualified to perform in routine clinical practice. A detailed knowledge of the protocol, the investigational product, or the investigator's brochure should not be needed to perform these tasks.[21]

Trial-specific activities delegated to local HCPs may include, for example:

- Referring potential participants for the trial to trial personnel for determination of trial eligibility
- Collecting routine clinical data for the trial (e.g., vital signs) in a template provided in the EHR

[19] See 21 CFR 312.3 (for definitions of the terms investigator and subinvestigator).

[20] See the information sheet guidance for sponsors, clinical investigators, and institutional review boards *Frequently Asked Questions – Statement of Investigator (Form FDA 1572)* (June 2010).

[21] Local HCPs can also be utilized in clinical trials with decentralized elements. See the guidance for industry, investigators, and other stakeholders *Conducting Clinical Trials With Decentralized Elements*.

- Following prompts in the EHR to document specified clinical events (e.g., death, myocardial infarction, stroke, seizure)

- Performing routine medical procedures (e.g., blood draws, radiographs, vital sign measurements, clinical examinations) at times specified in the protocol

It may be appropriate to engage local HCPs who are specialists in performing certain procedures (e.g., endoscopy, cardiac catheterization, biopsy) provided these procedures are within the scope of their practice and expertise. Such procedures should be covered by agreements between sponsors or investigators and health care institutions, local HCPs, and medical practices as applicable. (See section A.1.) Investigators should ensure that the reports from local HCPs who perform these procedures include the name of the local HCP and the dates that these procedures were performed.

B. Streamlining RCTs To Align With Clinical Practice

Trials that are most likely to be successfully integrated into clinical practice are those where the data needed for such trials are collected routinely in clinical practice visits with minimal need for protocol-specified procedures or additional visits. It may not be feasible for all trial procedures to be performed by local HCPs during routine care visits, and in these situations, sponsors can consider a hybrid approach, combining data contributed by local HCPs with study-specific procedures performed by trial personnel.

For trials integrated into clinical practice, the protocol should specify trial-specific activities that can be performed by local HCPs (e.g., obtaining routine laboratory tests or imaging at protocol-specified times).

IV. USING A QUALITY BY DESIGN APPROACH

QbD[22] involves incorporating quality into the design of clinical trials by identifying critical-to-quality factors (i.e., those that are likely to have a meaningful impact on participant's rights, safety and well-being and the reliability of the results), while eliminating procedures and processes that do not contribute to these primary goals. Simplifying trial designs by using these QbD principles is important for successful integration into clinical practice.

Sponsors must ensure the quality, integrity, and accuracy of the trial data.[23] Sponsors should build appropriate flexibility into trial protocols conducted in whole or in part in clinical practice to accommodate, for example, potential differences in the collection of data in clinical practice or performance of clinical care. This approach can include establishing trial visit windows that largely align with routine clinical practice visits.

[22] See the ICH guidance for industry *E8(R1) General Considerations for Clinical Studies* (April 2022).

[23] See 21 CFR 312.50 and 312.56.

It may be necessary to supplement data collected from clinical practice with procedures performed by investigators or subinvestigators or other trial personnel when the study procedures cannot be integrated into clinical practice without significant disruption to routine clinical workflows.

The sponsor is responsible for monitoring the trial to ensure that it is conducted in accordance with the protocol and FDA regulations, including requirements related to good clinical practice.[24] Remote (including centralized) and/or onsite monitoring should be risk-based and should address the critical-to-quality factors that are needed to generate reliable results and ensure the safety of participants.[25]

In designing protocols using a QbD approach, sponsors may wish to engage FDA, clinicians, patients, and other interested parties early to discuss trial design, data quality considerations, and operational issues. Important components of a QbD approach are discussed below.

A. Identifying the Trial Population

Eligibility criteria are intended to ensure that the trial population has the disease or condition to be studied and that only individuals for whom participation in the trial is safe are enrolled. For trials integrated into clinical practice, eligibility criteria should be minimal and straightforward, without compromising the ability to identify the appropriate population for the trial. Sponsors should attempt to align eligibility criteria with data that are routinely obtained in clinical practice. Eligibility can depend on objective data, including laboratory tests (e.g., microbiological culture, histopathology), physiological tests (e.g., blood pressure, tests of pulmonary function), and/or clinical imaging (e.g., CT scans, radiographs, and echocardiograms) that are routinely collected in clinical practice. Clinical evaluations that are well standardized and unlikely to vary can also be suitable as eligibility criteria. Simple, streamlined criteria that correctly identify the target population can enhance the feasibility and accuracy of enrollment, minimizing randomization of ineligible participants.

During protocol development, getting feedback from the medical community on the proposed protocol eligibility criteria can minimize the need for additional training and facilitate integration of clinical research into clinical practice.

B. Obtaining Informed Consent

There are various regulations regarding human subject protection and oversight by institutional review boards that are applicable when conducting a trial, including a trial integrated into clinical practice. Investigators must generally obtain informed consent from participants in a clinical

[24] See 21 CFR 312.50 and 312.56.

[25] See the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013) and the guidance for industry *A Risk-Based Approach to Monitoring of Clinical Investigations: Questions and Answers* (April 2023).

trial, consistent with the requirements in 21 CFR part 50,[26] and ensure that an institutional review board that complies with the requirements in 21 CFR part 56 will oversee the clinical study.[27] In addition, because protected health information may be part of trials, including those conducted in clinical practice, investigators should consider any additional requirements that may be relevant under the Health Insurance Portability and Accountability Act of 1996 (HIPAA).[28]

Informed consent documents for a trial can be embedded in EHRs, akin to how clinical informed consent documents can be embedded in EHRs for patients undergoing surgery or other procedures. Other electronic or paper-based processes for informed consent may also be appropriate.

C. Choosing Suitable Investigational Drugs

Drugs that are already FDA-approved for an intended use have better established safety profiles and are generally more suitable for use in trials integrated into clinical practice than drugs that are unapproved for any use. An approved product's well-characterized safety profile for the approved use may mean that limited collection of safety data for the unapproved use may be appropriate in certain circumstances. For example, when using an FDA-approved drug, it may be appropriate to consider selective collection of safety data, such as serious adverse events, adverse events of special interest, and adverse events that lead to discontinuation of the drug or withdrawal from the trial without the need to collect nonserious adverse events that are already well characterized.[29,30] Sponsors should consult with the relevant FDA review division to determine whether a selective approach to safety data collection would be appropriate.

FDA-approved drugs may still need a more robust safety evaluation if there are new concerns raised by their use in a novel combination or use in a new population or indication.

In some cases, it may be possible to study unapproved drugs with well-understood safety profiles in clinical practice environments (e.g., those that are members of an existing class, those where safety is already well characterized from prior trials). Sponsors should consult with the FDA review division to determine if a particular practice environment is suitable for trials with these types of drugs.

Trials involving approved or unapproved drugs with narrow therapeutic windows requiring therapeutic dose monitoring, those with complex dosing or administration regimens, those

[26] See 21 CFR 50.20 and 312.60.

[27] See 21 CFR 56.109, 56.111, and 312.66.

[28] Public Law 104-191.

[29] See the guidance for industry *Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations* (February 2016).

[30] See the ICH guidance for industry *E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials* (December 2022).

requiring special reconstitution processes, or those requiring specialized storage conditions might not be suitable for integration into clinical practice.

D. Randomization and Blinding

Randomization is the best available method to balance baseline prognostic factors between the treated and control groups, thereby reducing the potential for bias due to confounding and allowing for interpretable statistical analysis and inference.

Blinding is important to control for bias after enrollment, ensuring that outcome assessments, patient evaluations, clinical management, patient adherence, and lifestyle changes are not altered by knowledge of the treatment assignment. Even in trials with objective endpoints (e.g., death, hospitalization, stroke, or viral load), there is a risk that knowledge of the treatment assignment by the patient and/or provider may influence behaviors in ways that could affect the likelihood of an outcome (e.g., attention to diet and exercise, adherence to treatment, intensity of clinical monitoring).

Nonetheless, blinding may complicate efforts to integrate trials into clinical practice by adding complexity to trial implementation, requiring greater site resources, increasing trial costs, and requiring longer timelines to obtain blinded supplies and develop appropriate channels for trial drug delivery. As in any trial, when blinding is not feasible, it is important to identify potential sources of bias and to include measures to address these in the design of the trial to the extent possible (e.g., blinded and/or independent central review committee for assessments of outcome or use of objective outcome measures).

E. Comorbidities and Concomitant Medications

Health care systems may include diverse clinical populations with various comorbidities who take concomitant medications. These participants may be more representative of the patients who may take the drug if approved. However, managing concomitant medication use may be more challenging in routine clinical practice settings. When scientifically justified, a protocol may specify concomitant medications that cannot be used during the trial because of safety concerns. It may be difficult in a clinical practice setting to ensure that trial participants are not prescribed excluded concomitant medications. Use of automated messages in the EHR might help flag concomitant medications that are not allowed by the protocol when these are being prescribed by local HCPs as part of clinical practice. If there is a significant concern about managing concomitant medications, then the study may not be appropriate for integration with routine practice.

F. Study Endpoints

Outcomes that are based on significant medical events that typically lead to acute care (such as strokes, fractures, and myocardial infarctions) are more readily captured in routine clinical practice records. Some acute events may result in hospitalization outside of the patients' usual

health care systems. To maintain adequate and accurate case histories, investigators should attempt to get access to those medical records.[31]

Common clinical laboratory measurements and/or physiological measurements that are standardized and routinely collected for certain conditions (e.g., measurements of cholesterol, glycosylated hemoglobin, weight, blood pressure) may be appropriate outcomes to capture from clinical practice, and it may be feasible to assess and compare changes in these markers over time.

In practice, physicians may change the frequency of clinical or laboratory measurements depending on the clinical response (e.g., less frequent visits and subsequent measurements if the disease or condition is well controlled, more frequent visits and measurements if it is not well controlled), potentially resulting in imbalances in data collection when measurement intervals are not standardized. The trial protocol should address this potential imbalance by ensuring reasonably consistent frequency of clinical and biomarker measurements by trial personnel or local HCPs.

Many clinical trials rely on clinical outcome assessments (COAs), including clinician-reported outcomes and patient-reported outcomes, to assess patients' functional status or symptoms (e.g., mobility, pain, or mood). Because evaluating changes in functional status or symptoms will often require research-specific instruments and specific timing of assessments,[32] trials relying on such assessments may be more challenging to integrate into clinical practice. Using COAs that are most consistent with information collected in the context of a routine clinical practice visit, utilizing simple data entry, and avoiding any COA instruments requiring more complex patient assessments or extensive data collection could improve feasibility.

G. Adverse Events

As noted above, for FDA-approved (or in some instances unapproved) drugs with better-established safety profiles, it may be appropriate to selectively collect safety data, such as serious adverse events, adverse events of special interest, and adverse events that lead to discontinuation of the drug or withdrawal from the trial without collecting nonserious adverse events that are already well characterized. When the trial protocol relies on routine health care visits with local HCPs, additional procedures, such as real-time monitoring of patients' EHRs and/or periodic follow-up calls to study participants by trial personnel,[33] can be included to identify the adverse

[31] See the guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products*.

[32] See the draft guidance for industry *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making* (April 2023). When final, this guidance will represent FDA's current thinking on this topic.

[33] For example, in the Salford asthma study, safety monitoring was done by continuous, real-time monitoring of patients' EHRs and by telephone every 3 months. See Woodcock, A, J Vestbo, ND Bakerly, J New, JM Gibson, S McCorkindale, R Jones, S Collier, J Lay-Flurrie, L Frith, L Jacques, JL Fletcher, C Harvey, H Svedsater, and D Leather, on behalf of the Salford Lung Study Investigators, 2017, Effectiveness of Fluticasone Furoate Plus

events listed above. It may also be helpful to include automated notifications in EHR systems for local HCPs that the patient is a participant in a trial. Automated notifications may be used to flag abnormal laboratory results of concern and to describe adverse events that might be anticipated.

Sponsors are responsible for promptly reporting serious and unexpected suspected adverse events to FDA.[34] Oversight by the investigator will be critical to ensure that safety reporting requirements are met,[35] that responses to safety signals are appropriate, and that adverse events are managed as specified in the protocol.

The clinical trial protocol must specify measures taken to monitor the effects of the drug and to minimize the risk to participants.[36] The protocol should specify procedures for investigators and other trial personnel to evaluate adverse events and report adverse events to the sponsor.[37]

As in any trial, participants experiencing concerning signs, symptoms, or abnormal clinical events (e.g., hypoglycemia, abnormal cardiac rhythm) may seek medical attention, either within or outside the health care system in which the trial has been integrated. Participants should be instructed to report any acute care they receive to trial personnel. Easily accessible reporting methods, such as a trial helpline or patient portal, will facilitate more complete reporting by trial participants to trial personnel. With the permission of trial participants, investigators or other trial personnel should attempt to obtain reports of medical attention (e.g., emergency room visits, radiology reports, laboratory tests) that are relevant to the trial.

H. Data Privacy and Security

Access to data on trial participants should be restricted to authorized parties, and cybersecurity controls should be in place. In trials that make use of EHRs, data privacy and security are reliant on the use of safeguards in these systems, and sponsors should refer to the guidance for industry *Use of Electronic Health Record Data in Clinical Investigations* (July 2018).

Informed consent documents should reflect who will have access to a trial participant's data as part of the trial (see section IV.B).

Vilanterol on Asthma Control in Clinical Practice: An Open-Label, Parallel Group, Randomised Controlled Trial, Lancet, 390(10109):2247–2255.

[34] 21 CFR 312.32(c).

[35] See 21 CFR 312.32.

[36] 21 CFR 312.23(a)(6)(iii)(g).

[37] See ICH E6(R3); see also the web page Regulations: Good Clinical Practice and Clinical Trials, available at https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials (for links to FDA regulations related to human subject protection and the conduct of clinical trials).

I. Inspections

The goals of the bioresearch monitoring program are to protect the rights, safety, and welfare of research subjects; to verify the accuracy, reliability, and integrity of clinical and nonclinical trial data submitted to FDA; and to assess compliance with FDA's regulations governing the conduct of clinical and nonclinical trials, including regulations for informed consent and ethical review, and certain postmarketing requirements. To achieve these goals, bioresearch monitoring inspections by FDA assess practices and procedures likely to have a meaningful impact on the reliability of the results and on the rights, safety, and well-being of participants. Inspections also assess whether important protocol deviations occurred during a trial (e.g., failing to obtain informed consent, randomizing patients who did not meet enrollment criteria, failing to report important safety events) and any systemic or serious issues that occurred during the conduct of the trial.[38]

The sponsor must ensure that source records (or certified copies of source records) to support clinical trial data submitted to FDA are available for review by FDA upon request.[39] Records must be maintained and retained in compliance with FDA regulations.[40]

[38] Bioresearch Monitoring Program Compliance Programs web page, available at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs.

[39] See 21 CFR 312.58(a).

[40] See, e.g., 21 CFR 312.57 and 312.62.