U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

CDER Center for Clinical Trial Innovation (C3TI)

White Paper:

Selective Safety Data Collection

Disclaimer: This white paper is for discussion purposes only and does not represent draft or final guidance.

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Contents

1. Introduction

Development of a drug or biologic for diagnosis, cure, mitigation, treatment, or prevention of a disease or medical condition requires extensive pre-clinical and clinical investigations to determine that the medical product is effective and safe for its intended use. To gain approval for marketing in the United States by the Food and Drug Administration (FDA), sponsors of a marketing application must meet the statutory requirement for demonstration of substantial evidence of effectiveness.[1] Such marketing applications also contain extensive safety information on the drug collected throughout its lifecycle to enable the FDA to make a benefit-risk determination (see FDA guidance for industry, *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023)).

Early in development, sponsors collect a large amount of safety data from study participants, including physical examinations, extensive laboratory tests, x-rays, electrocardiograms, and other tests deemed necessary based on potential safety signals identified in nonclinical tests or knowledge of the drug's pharmacologic action. Comprehensive safety data collection may require many tests performed on the study participant and frequent study visits. As knowledge of the drug's safety profile evolves based on results from: (1) nonclinical studies; (2) clinical pharmacology studies, including an understanding of the drug's absorption, distribution, metabolism, and excretion, drug-drug interactions, and dose-and exposure-response relationships; and (3) completed and ongoing clinical trials, safety data collection may become more focused in later stage clinical investigations.

Selective safety data collection (SSDC) refers to a planned reduction in the collection of certain types of data in a clinical investigation for drugs with a well-characterized safety profile and for which the continued collection of common, non-serious adverse events (AEs) or routine laboratory assessments is unlikely to provide additional knowledge of clinical importance. SSDC facilitates efficiency in the conduct of large clinical trials designed to answer important scientific questions about the clinical benefits and/or safety of a drug. In reducing or eliminating the collection of unnecessary tests, procedures, and planned study site visits, several parties will likely benefit. For study participants, fewer blood draws, lab tests, or study visits may enable a higher rate of study enrollment and retention because of reduced participation burden. For investigators, a more streamlined clinical study protocol reduces complexity in study implementation, enabling study site personnel to focus on collection and assessment of information relevant to the study objective. For sponsors, it reduces study costs and incentivizes the conduct of adequate and well-controlled studies. For regulators, it enables reviewers to focus on relevant data that will inform the benefit-risk evaluation of the marketing application.

1 As described under 21 U.S.C. § 355(d) and Section 115(a) of the Food and Drug Administration Modernization Act (FDAMA).

FDA's willingness to apply SSDC in clinical trials was outlined in its guidance for industry, *Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval* Clinical Investigations (February 2016). This guidance (hereafter referred to as the February 2016 FDA guidance) described the types of clinical investigations that could employ SSDC (e.g., clinical investigations of new indications of approved drugs), types of safety data that could be considered for reduced collection, types of safety data that should always be collected, and different implementation approaches. Although sponsors could cite this guidance to support their plans to implement SSDC in a clinical trial, the guidance also noted that the FDA recommendations for SSDC might not align with the expectations of safety data collection in other regions or countries. Given that many large clinical trials are multi-regional, lack of harmonization on the SSDC principles across regulatory agencies was a barrier to efficiency in the conduct of clinical trials.

In 2017, the International Council for Harmonisation (ICH), a non-profit organization with representation from several regulatory agencies and industry associations, approved the formation of the ICH E19 Expert Work Group (EWG), whose objective was to develop a guideline for implementing SSDC in late-stage and post-approval clinical trials that could be endorsed by all its representative members for use across multiple regions and countries. The ICH E19 EWG was led by FDA and had representation from the founding regulatory members, the United States, European Commission (EC), and Japan (MHLW/PMDA), their industry associations, and other regulatory agencies. On September 27, 2022, the ICH guidance for industry, *E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials*, was finalized. ICH E19 captured most recommendations put forward in the February 2016 FDA guidance and provided more details on factors that could contribute to determining whether a drug's safety profile was sufficiently characterized to justify SSDC. Both documents emphasize the importance of early consultation with regulatory authorities and reaching agreement on a study protocol that will outline how SSDC will be implemented in the clinical trial, and that SSDC does not entail altering local/regional safety reporting requirements or affect the responsibilities of investigators as health care professionals to monitor trial participants and ensure their treatment according to prevailing standards of care.

SSDC does not mean the elimination of or reduction in collection of data that are necessary to ensure study participant safety, including comprehensive evaluation and baseline assessments of study participants. Furthermore, certain information should continue to be collected throughout the clinical trial; for example, the occurrence of a serious adverse event (SAE)[2] or an AE resulting in study drug discontinuation should be reported to regulatory authorities.

2 A serious adverse event is an adverse event that results in any of the following: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity of substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/ birth defect (21 CFR 312.32 or ICH E2A).

FDA implemented ICH E19 with the publication of the guidance for industry, *E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials* (December 2022). Other regulatory agencies have also implemented E19, including those representing Canada, China, Egypt,Europe, Japan, Singapore, and Taiwan, while additional countries are in the implementation process.[3] In this white paper, we discuss how SSDC has evolved over the past 10 to 15 years and what we hope to achieve in the coming years with global harmonization of the approach to implementing SSDC in clinical trials designed to evaluate long-term benefits and risks of medical products.

2. Past Experience with Selective Safety Data Collection

SSDC in clinical trials has been employed in different therapeutic areas for many years. In 2001, to facilitate the development of new therapies for life-threatening diseases such as cancer, FDA issued a guidance for industry, *Cancer Drug and Biological Products – Clinical Data in Marketing Applications (October 2001)*, which discussed the data types that should be collected or could be reduced/eliminated and in which types of marketing applications (e.g., initial marketing applications versus efficacy supplements). SSDC was not specifically discussed in this guidance, however, and in 2013 FDA published a draft guidance followed by the final February 2016 FDA guidance that introduced the SSDC terminology.

To evaluate the extent to which SSDC has been used in clinical trials, Yamatani and colleagues reported their findings from a systematic literature search of clinical trials published in the New England Journal of Medicine from February 1, 2016, to December 31, 2019, coinciding with the February 2016 guidance publication and several months after the issuance of the ICH E19 draft guideline for public comment in April 2019 (Yamatani et al. 2022). The authors identified 459 trials of medicinal products published during this timeframe. Of these, 44 (9.6%) included one or more features identified as SSDC as described in the ICH E19 draft guideline. Most trials were for cardiovascular diseases (54.5%), followed by infectious diseases (18.2%), other (15.9%), and oncological diseases (11.4%). No trials were conducted in support of an initial marketing application submission, and 41 (93.2%) of the trials were initiated before 2017, including 15 (34.1%) between 2000 and 2011, well before the issuance of the February 2016 FDA guidance.

The report identified three clinical trials the authors described as effectively applying SSDC: the NAVIGATE ESUS trial (Hart et al. 2018), the EXSCEL trial (Holman et al. 2017), and the IRIS trial (Hochhaus et al. 2017). However, the Supplementary Appendix also identified trials that supported important expanded indications, including the DAPA-HF trial, which extended the use of dapagliflozin

3 See ICH Efficacy Guidelines, available at: https://www.ich.org/page/efficacy-guidelines

(initially approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus) to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with reduced ejection fraction (McMurray et al. 2019). The DAPA-HF trial prespecified collection of SAEs, AEs associated with study drug discontinuation, and AEs and laboratory events of special interest. Data on other AEs (i.e., non-serious) were not routinely collected given extensive safety data collection in prior dapagliflozin clinical trials.

Despite experience with SSDC in many large clinical trials, one concern is that reduced collection of certain events might result in an inadequate safety database to inform the benefit-risk assessment. Comments received after release of the draft ICH E19 guideline captured some of these sentiments and prompted revision of the guideline to reach Step 4 finalization.[4] However, concerns remain over adopting SSDC in clinical trials despite a well-characterized safety profile of the investigational drug, including inability to provide updated safety information to product labeling.

To determine whether comprehensive safety data collection results in additional new safety information to product labeling, FDA researchers retrospectively assessed safety data collection for clinical trials that supported marketing applications for expanded indications approved after 2016. The assessment focused on submissions that could have adopted SSDC but did not, and examined whether detailed safety data collection resulted in any change to the safety label or impacted the benefit-risk assessment.

This research project is ongoing; however, the submission of tocilizumab to treat giant cell arteritis (GCA) is an example of a submission that might have adopted SSDC but did not. Originally approved in the United States for use in adults with moderately-to-severely active rheumatoid arthritis (RA) who had an inadequate response to one or more TNF-antagonist therapies, tocilizumab was later developed for GCA.[5,6] The sponsor proposed a phase 3, multicenter, randomized, double-blind, placebo-controlled study in 251 patients diagnosed with GCA to evaluate tocilizumab's efficacy as measured by the proportion of patients in sustained remission at week 52 following induction and adherence to the protocol-defined prednisone taper regimen (Stone et al. 2017).

The sponsor's clinical development program in the adult RA study population included five pivotal phase 3 trials and three long-term extension studies. The cumulative safety data reflected the experience of 4,009 patients and 14,994 patient-years of study at the time the GCA protocol was submitted, and suggested that adverse effects were manageable, reversible, and usually not treatment-limiting. RA and GCA were considered sufficiently similar conditions

4 See Overview of Comments Received on ICH Guideline E19 on Optimisation of Safety Data Collection, available at: https://www.ema.europa.eu/en/documents/comments/overview-comments-received-draft-ich-guideline-e19-optimisation-safety-data-collection-step-2b_en.pdf

5 See FDA medical review for supplemental approval of BLA 125276/S-112, available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/125276Orig1s112.pdf

6 See Actemra (tocilizumab) injection prescribing information, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125276s144,125472s056lbl.pdf

to assume that a similar risk-benefit ratio would be observed in the GCA trial. Despite the existing safety data and the anticipated similarity of the populations under study, SSDC was not implemented. Safety data were collected at study weeks 4, 8, and subsequent 8-week intervals and included hematology, serum chemistry, liver profile, and lipid panel and HbA1c. Ultimately, tocilizumab was approved to treat GCA in adults with no modifications to the safety sections of the label.

3. Current Experience with Selective Safety Data Collection

Since the finalization of ICH E19 and its implementation by several regulatory agencies, the community does not know the extent to which sponsors have applied SSDC to clinical trials, the therapeutic areas, the settings (i.e., pre-approval or post-approval), the challenges sponsors have encountered (including agreement with regulatory authorities), and the efficiencies that have been observed in trials using SSDC. There is no database that systematically captures this information to analyze the types of trials, methodologies, and outcomes that incorporate SSDC, nor is there a way to share experience across multiple parties. In FDA's interactions with sponsors and their drug development programs, we are aware of several ongoing trials that have incorporated SSDC and describe these below.

3.1. Selective Safety Data Collection in Oncology

Pragmatica-Lung Study (NCT05633602)

Oncology may be considered a challenging therapeutic space in which to deploy selective safety reporting, given the high burden of toxicity that can occur with anti-cancer treatments. Nonetheless, the principles of ICH E19 have been successfully applied; for example, the ongoing Pragmatica-Lung Study, sponsored by the U.S. National Cancer Institute (NCI) and catalyzed through efforts to modernize clinical trials by the NCI and FDA's Oncology Center of Excellence (OCE), is an excellent example of how the principles of ICH E19 may be applied to prospective trial design by taking a simpler, more pragmatic approach to safety data collection (Patel et al. 2024; Reckamp et al. 2024).[7] The primary study objective of Pragmatica-Lung is to compare overall survival in participants previously treated with platinum-based chemotherapy and immunotherapy for stage IV or recurrent non-small cell lung cancer randomly assigned to pembrolizumab and ramucirumab versus standard of care. The secondary objective is to summarize reports of serious and unexpected high-grade (≥ grade 3) treatment-related AEs determined by the physician within each treatment arm. In this study, safety data collection is limited to significant AEs of

7 Pragmatica-Lung Cancer Treatment Trial, National Cancer Institute at the National Institutes of Health, posted March 9, 2023, available at: https://www.cancer.gov/types/lung/research/pragmatica-lung-cancer-trial

grade 3 or higher severity, as well as fatalities, given the well-established side effect profiles of pembrolizumab and ramucirumab. Grade 1 to 2 and non-serious and/or expected grade 3 or 4 AEs are not required to be collected, aligning with SSDC outlined in ICH E19. Collection of concomitant medications was limited to as needed on a clinical basis. Several factors contributed to the acceptability of this selective approach. First, the safety profiles of both pembrolizumab and ramucirumab, as well as the comparator standard of care drugs, are well established as already approved therapies across multiple cancer indications. In addition, complete safety data of the combination of pembrolizumab and ramucirumab compared to investigator's choice of standard of care chemotherapy had already been elucidated by a smaller randomized trial (Reckamp et al. 2022) that generated results suggesting an overall survival benefit that led to the hypothesis and subsequent design of Pragmatica Lung. Importantly, selective safety reporting is only one pragmatic element in this study which also includes broad eligibility, optimization of community recruitment strategies, and omission of protocol-required disease assessments (e.g., follow up consistent with routine care).

3.2. Selective Safety Data Collection in Cardiometabolic Diseases

VICTORION-2-PREVENT (NCT05030428)

As observed by Yamatani et al., most clinical trials employing SSDC are in the cardiovascular disease therapeutic area. VICTORION-2-PREVENT is an ongoing, randomized, double-blind, placebo-controlled, multicenter trial assessing the impact of inclisiran on major cardiovascular events in participants with established cardiovascular disease, and an example of a trial that specified SSDC in its protocol submitted to the FDA. On December 22, 2021, FDA approved the New Drug Application (NDA) for Leqvio (inclisiran) as a small interfering ribonucleic acid (siRNA) therapy to lower low-density lipoprotein cholesterol (LDL-C). Leqvio is now indicated as an adjunct to diet and statin therapy to treat adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C. The U.S. approval was based on three placebo-controlled trials that included 1,833 patients treated with inclisiran, including 1, 682 exposed to the drug for 18 months.[8] Although the trial is being conducted post-approval, it was initiated before approval, as knowledge from the large phase 3 programs enabled the sponsor and FDA to agree that the risks of inclisiran were sufficiently characterized to apply SSDC. Furthermore, this trial is being conducted in over 1,100 sites across 40 countries. Each site allows for SSDC, which includes the collection of all SAEs and AEs leading to discontinuation but limits all other AEs to those of special interest and limited liver safety assessments in a subset of study participants. Implementing SSDC in VICTORION-2-PREVENT allowed for reduced frequency of study visits that more closely resembled clinical practice (see Table 1 below). Countries that did not accept implementation of SSDC did not participate in this trial.

8 See Leqvio (inclisiran) prescribing information, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/214012s011lbl.pdf

Table 1. VICTORION-2-PREVENT

	VICTORION-2-PREVENT Study	Standard Approach
Visit Frequency	Every 6 months	Monthly - Quarterly
General Safely Assessments		
SAEs	All SAEs	All SAEs
AEs	Only those leading to the drug d/c and AESI	All AEs
Vital signs, physical exam	At screening only	At all visits
Scheduled ECG	None	At all visits
Additional measures (e.g., QoL)	None	At all visits
Central Lab Safety Assessments		
Hematology, biochemistry, urinalysis	At screening only	At all visits
Lipid panel	Annually	At all visits
LFTs	In the subset of pts (20%) annually	In all pts at all visits
HIV & Hepatitis	None	At screening
Pregnancy test	At screening only	At all visits

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ECG, electrocardiogram; LFT, liver function test; SAE, serious adverse event; QoL, quality of life.

EMPA-KIDNEY and EMPACT-MI

Empagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor approved in 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2D) based on an extensive nonclinical and phase 2 and 3 clinical development program. At the time of approval, 8,400 patients had been exposed to any dose of empagliflozin in T2D trials, including 4,261 patients exposed for at least 1 year.[9] Two other SGLT2 inhibitors, also with extensive pre-market safety databases, had been approved before empagliflozin. Since these initial approvals for the SGLT2-inhibitors, several large outcome trials have been or are being conducted to assess efficacy in other conditions, including heart failure and chronic kidney disease in the diabetic and non-diabetic population.

Based on a well-established safety profile for empagliflozin with more than 16,000 patient-years of cumulative exposure in more than 10,000 individuals, SSDC was implemented in randomized, double-blind, placebo-controlled, multicenter trials assessing the safety and efficacy of empagliflozin in participants with chronic kidney disease (EMPA-KIDNEY) and in patients hospitalized for myocardial infarction (EMPACT-MI). EMPA-KIDNEY limited collection of non-serious events to those that led to discontinuation of study treatment, as well as selected events of interest, including bone fracture, severe hypoglycemia, liver injury, and lower limb amputations (see Table 2 below) (EMPA-KIDNEY Collaborative Group 2022; Harrington et al. 2022).

9 See FDA medical review for initial approval of NDA 204629, available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204629Orig1s000MedR.pdf

Table 2. EMPEROR, EMPA-KIDNEY, and EMPACT-MI

	EMPEROR (Reduced and Preserved)	EMPA-KIDNEY	EMPACT-MI
Clinic visit frequency	Clinic visits at screening, baseline, week 4, 12, 32, and 52, then every 24 weeks. Phone visits between clinic visits following week 12 visit.	Month 2 and 6, then every 6 months	One visit at 2 weeks after randomization (remote), at month 6 (clinic visit), then every 6 months (remote)
General Safely Assessments			
SAEs	All (clinic and phone)	All	All
AEs	All (clinic and phone)	SAEs and pre-specified non-SAEs (discontinuations, AESIs, fractures, hypoglycemia, gout, dehydration and leading to amputation)	SAEs, AESIs (AEs leading to lower limb amputation, contrast-induced acute kidney injury, hepatic injury, ketoacidosis) and AEs leading to treatment discontinuation of at least 7 consecutive days
Vital signs, physical signs	At all visits: blood pressure, pulse rate, and weight	BP and weight at all visits, hip and waist circumference at baseline, month 18, and EOS	At randomization
Scheduled ECG	At screening and end-of-treatment (EOT)	Not collected	None
Additional measures (e.g., QOL)	KCCQ: baseline, week 32 and 52, EOT, and EOT +30 days; EQ-5D additionally week 100 and 148 where available.	EQ-5D at baseline, month 18, and EOS	None
Other	NYHA, health care resource utilization, concomitant therapies: at all clinic visits	None	None

	EMPEROR (Reduced and Preserved)	EMPA-KIDNEY	EMPACT-MI
Central Lab Safety Assessments			
Hematology, biochemistry, urinalysis	All clinic visits: Hematocrit, hemoglobin, reticulocyte count (reflex test if Hb outside normal range), RBC, WBC, platelet count / thrombocytes, differential automatic (relative and absolute count): neutrophils, eosinophils, basophils, monocytes, lymphocytes Albumin, alkaline phosphatase, γ-GT (reflex test triggered by elevated alkaline phosphatase on two sequential measures), ALT (alanine transaminase, SGPT), AST (aspartate transaminase, SGOT), bicarbonate, bilirubin total, fractionated if increased, calcium, chloride, creatinine, CK, Hs troponin I (reflex tests if CK is elevated), glucose, magnesium, phosphate, potassium, protein total, sodium, Urea (BUN), uric acid	Creatinine at all visits (central and local), UACR (central) at baseline, month 2 and 18, and EOS, potassium (local) at all visits, Hb and Hct (local) at baseline (all) and month 18 (UK only), Sodium/calcium/ phosphate (local) at month 18 only (UK only)	Serum creatinine at randomization (local lab), during follow up – only in subset of countries where it was requested by regulatory authorities. Hemoglobin, LDL cholesterol, uric acid, potassium from index hospitalization (baseline) if available only

	EMPEROR (Reduced and Preserved)	EMPA-KIDNEY	EMPACT-MI
Lipid panel	Baseline, week 52 and 100, EOT cholesterol (total), HDL cholesterol, calculated LDL cholesterol, triglycerides (reflex test for direct measurement of LDL cholesterol triggered if triglycerides are >400 mg/dl or 4.52 mmol/l)	None	None
LFTs	All clinic visits	At all visits, local labs only	None
Pregnancy test	All clinic visits (local required only), for female patients of child-bearing potential. More frequent testing should be performed if required by local regulations/authorities.	At all visits, if pregnancy reasonably possible or if required by local regulations	At screening and at EOS
Other	eGFR, UACR: all visits NT-proBNP: baseline, week 4, 12, 32, and 52, and EOT HbA1c: baseline, week 12, then all visits High-sensitivity Troponin T: only baseline	NT-pro-BNP (central) baseline only, HbA1c (central) at baseline, month 2 and 18, and EOS	NT-proBNP/BNP and HbA1c from index hospitalization (baseline) if available only

Abbreviations: γ-GT, gamma-glutamyl transferase; AE, adverse event; AESI, adverse event of special interest; BP, blood pressure; BUN, blood urea nitrogen; CK, creatine kinase; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EOS, end-of-study; EOT, end-of-treatment; Hb, hemoglobin; Hct, hematocrit; HDL, high-density lipoprotein; KCCQ, Kansas City Cardiomyopathy Questionnaire; LDL, low-density lipoprotein; LFT, liver function test; NYHA, New York Heart Association; QOL, quality of life; RBC, red blood cell; SAE, serious adverse event; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; UACR, urine albumin-creatinine ratio; WBC, white blood cell.

EMPACT-MI streamlined data collection throughout the trial and limited collection of non-serious events to those of special interest (e.g., ketoacidosis, lower limb amputations, contrast-induced kidney injury, and liver injury) and those leading to treatment discontinuation (see Table 2). A focused form of safety data collection enabled streamlined patient follow-up, introduced remote patient follow-up, and reduced the overall burden on investigators and patients.

SSDC in EMPA-KIDNEY was initially proposed by the academic partners engaged in the trial and supported by the sponsor. Comfort with the approach led to more comprehensive streamlining of data collection in EMPACT-MI, including SSDC. The sponsor team noted that SSDC facilitated streamlined and remote patient follow-up and meaningfully reduced the burden for investigators and patients. The approach was not, however, accepted by all health authorities. Eight of 22 countries in Asia, Europe, and Latin America requested local protocol amendments that included, for example, mandatory collection of information about serum creatinine during patients' follow-up for regular assessment of estimated glomerular filtration rate or collection of all AEs instead of focused safety event collection. Based on their experience, the sponsor noted key barriers to the widespread use of SSDC approaches. First, the lack of harmonized regulatory guidelines on acceptance of SSDC increases the likelihood of delays in Clinical Trial Application/Investigational New Drug approvals, requests for local amendments, and potential delays in the NDA approval. In addition, there is limited awareness of examples of SSDC acceptance by health authorities. Finally, companies have concerns that data waived from collection by one health authority may be requested by another health authority during their review.

4. Opportunities for Expanded Use of Selective Safety Data Collection in Clinical Trials

As demonstrated by Yamatani et al., as well as current experience with the trials discussed above, sponsors and regulatory authorities have accepted the use of SSDC in clinical trials, but uptake may be limited. At an FDA-led scientific session at the 2024 Drug Information Association Annual Meeting, representatives from FDA, Health Canada, the European Medicines Agency, and industry (Novartis) discussed their experience with implementation of the E19 guideline. Although this session generated much interest from the audience, it was apparent that unawareness of E19 signals the need for broader dissemination of the guideline and shared lessons learned from sponsors and regulators who have experience with SSDC in clinical trials.

The CDER Center for Clinical Trial Innovation (C3TI), with a mission to promote clinical trial innovation through enhanced communication and collaboration, can help expand appropriate use of SSDC in clinical trials through its Demonstration Program. This program aims to connect CDER staff, including review team members and relevant subject-matter experts, with sponsors to strategically streamline data collection in some late-stage pre-approval or post-approval trials.[10]

As experience gained from SSDC applied across therapeutic areas and types of trials increases, sponsors and regulators should share successes and challenges with these trials, as lessons learned from these experiences will help overcome barriers to efficient drug development and facilitate faster access to safe and effective medicines.

10 See C3TI Demonstration Program, accessible at: https://www.fda.gov/about-fda/cder-center-clinical-trial-innovation-c3ti/c3ti-demonstration-program

5. References

Guidances

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).

FDA guidance for industry Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations (February 2016).

FDA guidance for industry Cancer Drug and Biological Products - Clinical Data in Marketing Applications (October 2001).

FDA guidance for industry Benefit-Risk Assessment for New Drug and Biological Products (October 2023).

Literature

EMPA-KIDNEY Collaborative Group, 2022, Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial, Nephrol Dial Transplant, 37(7):1317-1329.

Harrington, J, JA Udell, WS Jones, SD Anker, DL Bhatt, MC Petrie, O Vedin, M Sumin, I Zwiener, AF Hernandez, and J Butler, 2022, Empagliflozin in patients post myocardial infarction rationale and design of the EMPACT-MI trial, Am Heart J, 253:86-98.

Hart, RG, M Sharma, H Mundl, SE Kasner, SI Bangdiwala, SD Berkowitz, B Swaminathan, P Lavados, Y Wang, Y Wang, A Davalos, N Shamalov, R Mikulik, L Cunha, A Lindgren, A Arauz, W Lang, A Czlonkowska, J Eckstein, RJ Gagliardi, P Amarenco, SF Ameriso, T Tatlisumak, R Veltkamp, GJ Hankey, D Toni, D Bereczki, S Uchiyama, G Ntaios, BW Yoon, R Brouns, M Endres, KW Muir, N Bornstein, S Ozturk, MJ O'Donnell, MM De Vries Basson, G Pare, C Pater, B Kirsch, P Sheridan, G Peters, JI Weitz, WF Peacock, A Shoamanesh, OR Benavente, C Joyner, E Themeles, and SJ Connolly, 2018, Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source, N Engl J Med, 378(23):2191-2201.

Hochhaus, A, RA Larson, F Guilhot, JP Radich, S Branford, TP Hughes, M Baccarani, MW Deininger, F Cervantes, S Fujihara, CE Ortmann, HD Menssen, H Kantarjian, SG O'Brien, and BJ Druker, 2017, Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia, N Engl J Med, 376(10):917-927.

Holman, RR, MA Bethel, RJ Mentz, VP Thompson, Y Lokhnygina, JB Buse, JC Chan, J Choi, SM Gustavson, N Iqbal, AP Maggioni, SP Marso, P Öhman, NJ Pagidipati, N Poulter, A Ramachandran, B Zinman, and AF Hernandez, 2017, Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med, 377(13):1228-1239.

McMurray, JJV, SD Solomon, SE Inzucchi, L Køber, MN Kosiborod, FA Martinez, P Ponikowski, MS Sabatine, IS Anand, J Bělohlávek, M Böhm, CE Chiang, VK Chopra, RA de Boer, AS Desai, M Diez, J Drozdz, A Dukát, J Ge, JG Howlett, T Katova, M Kitakaze, CEA Ljungman, B Merkely, JC Nicolau, E O'Meara, MC Petrie, PN Vinh, M Schou, S Tereshchenko, S Verma, C Held, DL DeMets, KF Docherty, PS Jhund, O Bengtsson, M Sjöstrand, and AM Langkilde, 2019, Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction, N Engl J Med, 381(21):1995-2008.

Patel, TH, DR Rivera, H Singh, and PG Kluetz, 2024, When less is more-reducing complexity in cancer trials, Lancet Oncol, 25(1):10-12.

Reckamp, KL, MW Redman, KH Dragnev, WT Iams, BS Henick, J Miao, ML LeBlanc, DR Carrizosa, RS Herbst, CD Blanke, and JE Gray, 2024, SWOG S2302, PRAGMATICA-LUNG: A prospective randomized study of ramucirumab plus pembrolizumab (PR) versus standard of care (SOC) for participants previously treated with immunotherapy for stage IV or recurrent non-small cell lung cancer, Journal of Clinical Oncology, 42(16_suppl):TPS8657-TPS8657.

Reckamp, KL, MW Redman, KH Dragnev, K Minichiello, LC Villaruz, B Faller, T Al Baghdadi, S Hines, L Everhart, L Highleyman, V Papadimitrakopoulou, JW Neal, SN Waqar, JD Patel, JE Gray, DR Gandara, K Kelly, and RS Herbst, 2022, Phase II Randomized Study of Ramucirumab and Pembrolizumab Versus Standard of Care in Advanced Non-Small-Cell Lung Cancer Previously Treated With Immunotherapy-Lung-MAP S1800A, J Clin Oncol, 40(21):2295-2306.

Stone, JH, K Tuckwell, S Dimonaco, M Klearman, M Aringer, D Blockmans, E Brouwer, MC Cid, B Dasgupta, J Rech, C Salvarani, G Schett, H Schulze-Koops, R Spiera, SH Unizony, and N Collinson, 2017, Trial of Tocilizumab in Giant-Cell Arteritis, N Engl J Med, 377(4):317-328.

Yamatani, Y, H Saeki, R Tanaka, T Komeda, Y Watabe, and H Sakai, 2022, How Many Clinical Trials Exist that Have Adopted Selective Safety Data Collection? NEJM Literature Search Results: The Possibility of Harmonizing the ICH E19 Guideline, Therapeutic Innovation & Regulatory Science, 56(4):677-684.

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