REAL-WORLD EVIDENCE ALLIANCE

info@rwealliance.org
rwealliance.org

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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products; Draft Guidance for Industry; Availability (Docket No. FDA-2021-D-1214)

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to comment on the draft guidance entitled "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products" (referred to here as the "Draft Guidance").[1] We are a coalition of real-world data ("RWD") and analytics organizations with a common interest in harnessing the power of real-world evidence ("RWE") to inform regulatory decision-making to improve patients' lives. Our members have deep knowledge and experience working with healthcare data across disease areas and patient populations, and we aim to bring these collective insights to bear in support of RWE policies. [2]

The RWE Alliance envisions a future in which data generated in everyday clinical practice and everyday life through electronic health records ("EHRs"), administrative claims and billing data, product and disease registries, personal devices, wearables, and health applications will be used to generate evidence that complements clinical trial data to inform regulatory decisions. To achieve this goal, the RWE Alliance advocates for policies that will (1) advance FDA's RWE Framework, (2) encourage the use of RWE to better understand treatment effects in underrepresented populations, (3) enhance opportunities for RWE organizations to consult with FDA, and (4) increase communication on the generation and use of RWE.[3]

We commend FDA for issuing the Draft Guidance as part of the Agency's RWE Program, consistent with its mandate under the 21st Century Cures Act (the "Cures Act"), and for the Agency's overall efforts to develop four substantive draft guidance

[1] 86 Fed. Reg. 70132 (Dec. 9, 2021).

[2] For information about our members, please see our website, https://rwealliance.org/who-we-are/.

[3] Additional information about what we believe is available on our website, https://rwealliance.org/what-we-believe/.

documents on key RWD/E topics.[4] The RWE Alliance appreciates FDA's commitment to developing and implementing policies to ensure the RWD/E used in regulatory decision-making are transparent, auditable, reproducible, and scientifically valid. We share this goal, as these efforts will ultimately benefit patients.

RWD differ from traditional clinical trial data in how and why they are collected, curated, and analyzed. Due to these distinctions, RWD can have some important differences when compared with clinical trial data, while also offering unique advantages for drug development and regulatory decision-making. For example, RWD may be aggregated as a multipurpose dataset, which can provide insights for specific products that would not be apparent in clinical trial data. Often, clinical trial populations are not fully representative of relevant patient populations in real-world settings, and RWD can serve as a resource to generate evidence that complements clinical trials and provide insights about treatment heterogeneity in conditions of real-world use.

We are confident the use of RWE can be considered and accepted by FDA in a way that reflects both these advantages and unique considerations presented by RWD sources, without compromising the quality of the evidence used for regulatory decision-making. We envision that this framework would have the flexibility to account for and inform a wide range of ways in which RWD/E can be used in the regulatory process. As use of RWD/E in regulatory decision-making continues to expand, flexibility in the framework will be important for allowing FDA's approach for RWE studies to evolve with these further advances. We believe that regulatory expectations for RWE studies should be tailored to the unique advantages and considerations presented by RWD/E, which are distinct from those of traditional clinical trials. This approach will help ensure that regulations governing clinical trials are not applied in a way that imposes requirements that is duplicative or conflicts with requirements governing research. For this reason, we agree that directly applying FDA's requirements governing traditional clinical trials (including parts 50, 56, and 312) is not appropriate for many uses of RWE.

The following subsections provide our comments on specific regulatory topics discussed in the Draft Guidance.

I. Applicability of Parts 50, 56, and 312 to Non-Interventional Studies

We appreciate FDA's definitive statement that a non-interventional study is not a "clinical investigation" requiring an investigational new drug application ("IND") under part 312. The Draft Guidance defines "non-interventional study" as "a type of study in which patients received the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol."[5] We agree that such

[4] As FDA works to finalize each of the guidances, we recommend that the Agency consider cross-referencing relevant recommendations across the guidance documents to facilitate stakeholder understanding and use of these documents.

[5] Draft Guidance at Lines 66–68. The use of "received" in this definition implies that a patient always has already received the drug at the time the study begins, but this is not necessarily the case, especially in

use is explicitly carved out from the regulatory definition of a "clinical investigation" in part 312, which provides that "the use of a marketed drug in the course of medical practice" is not an experiment and thus not a clinical investigation.[6] Whether or not a study requires an IND, however, we believe it should be rigorously conducted to ensure quality and validity, such as by pre-specifying study hypotheses.

That said, the "interventional" versus "non-interventional" distinction does not always cleanly apply to RWD, given the various ways in which RWD can be used to advance medical product development and support evaluations of a product's benefits and risks.

Although we agree that non-interventional trials as defined in the Draft Guidance are not "clinical investigations" for purposes of part 312, it is unclear how FDA's proposed definitions of "non-interventional" and "interventional" studies otherwise align with its definitions of "clinical investigation" in parts 312, 50, and 56. For example, despite stating that FDA does not consider non-interventional studies, including "ancillary protocol-specified activities or procedures," to be "clinical investigations under part 312," the Agency also states that "sponsors must ensure that applicable requirements per FDA regulations under 21 CFR parts 50 . . . and 56" are met for these studies. The basis for FDA's conclusion—that a non-interventional study is not subject to part 312 but would be subject to parts 50 and 56—is unclear.

The final guidance would benefit from a more robust discussion of when FDA views an RWE study as a "clinical investigation" subject to part 312 and how FDA intends the definitions of interventional and non-interventional studies to intersect with the scope and applicability provisions of parts 312, 50, and 56. The final guidance also would benefit from more specific examples of RWE studies and whether FDA views those example studies as subject to parts 50, 56 and 312. Potential examples include a natural history of disease study involving blood draws beyond the standard of care; a study in which there are multiple approved treatment options within the standard of care that are equally indicated for a patient population, such that assigning a patient to one option does not necessarily result in the use of a different treatment than would have occurred outside of the study context; and hybrid studies combining non-interventional and interventional elements in the study design, such as pragmatic randomized trials. We would welcome the opportunity to provide additional input to the Agency as FDA

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prospective, non-interventional studies. We recommend clarifying this point by revising to say "*receive* the marketed drug of interest."

[6] 21 C.F.R. § 312.3(b). FDA's definition of RWD should use "routinely" to modify the provision of health care, not the collection of data. The defining quality of RWD is the context, not the frequency, in which the data are collected. As revised, the definition would read, "data relating to patient health status and/or the routine delivery of health care collected from a variety of sources." Additionally, in light of the ongoing COVID-19 public health emergency, we recommend clarifying explicitly in the final guidance that a study in which a product subject to an emergency use authorization is used in the course of medical practice would be a non-interventional study that does not require an IND. This clarification would be consistent with section 564(k) of the Federal Food, Drug, and Cosmetic Act.

considers the many potential types of RWE studies and when and how FDA's clinical trial regulations should apply to these studies.

Finally, in footnote 9 of the Draft Guidance, FDA states that non-interventional studies may be required by FDA as a postmarketing requirement ("PMR") or agreed upon between FDA and an applicant as a postmarketing commitment ("PMC").[7] FDA then indicates that "[s]uch studies carry specific obligations not addressed in this guidance."[8] Given the emphasis in the Cures Act regarding use of RWD/E for fulfillment of PMRs in particular, we urge FDA to provide more specific guidance on recommendations applying to PMRs and PMCs, and on using RWD/E to satisfy PMRs and PMCs more generally.

II. Standards for Approval and Licensure

The Draft Guidance states, "Regardless of a study's interventional or non-interventional design, the evidence submitted by a sponsor in a marketing application to support the safety and/or effectiveness of a drug must satisfy the applicable legal standards for the application to be approved or licensed."[9] We agree and encourage FDA to explain in the final guidance that RWE can be a valuable source of substantial evidence for regulatory decision-making.[10] Depending on the context in which it is used, RWE as part of a broader clinical data package may provide substantial evidence of effectiveness, or RWE may satisfy the substantial evidence standard on its own—including when a randomized clinical trial is not feasible, practicable, or ethical due to the therapeutic area or other limitations.[11]

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[7] Draft Guidance at n.9.

[8] *Id.*

[9] *Id.* at Lines 112–115.

[10] We recommend also including this discussion of how RWE can provide or contribute to substantial evidence in FDA's final version of the draft guidance entitled "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products." In this draft guidance, the Agency identified RWE as an example source of "[c]onfirmatory evidence." FDA, *Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, at 11 (Dec. 2019). We also recommend addressing this topic in FDA's planned guidance entitled "Meeting the Substantial Evidence Standard Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence." CDER Guidance Agenda, New & Revised Draft Guidance Documents Planned for Publication in Calendar Year 2022 (January 2022), https://www.fda.gov/media/134778/download.

[11] The Alliance also encourages FDA to use future guidance to address foundational concepts such as how a non-interventional study can be considered "adequate and well-controlled." This topic has been addressed by other stakeholders, and we encourage the Agency to build upon this prior work in future guidance. *See*, *e.g.*, Duke-Margolis Center for Health Policy, *Understanding the Need for Non-Interventional Studies Using Secondary Data to Generate Real-World Evidence for Regulatory Decision Making, and Demonstrating their Credibility* (Nov. 25, 2019), https://healthpolicy.duke.edu/sites/default/files/2020-08/Non-Interventional%20Study%20Credibility.pdf; Duke-Margolis Center for Health Policy, *Adding Real-World Evidence to a Totality of Evidence Approach*

FDA has broad authority and discretion to consider RWE when evaluating the effectiveness of a drug for an approval decision, as shown by recent examples. When FDA approved Prograf® (tacrolimus) for a new use to prevent organ rejection in patients receiving lung transplantation, RWD from a non-interventional study served as primary evidence for this approval; and, as the Agency press release explained, "randomized controlled trials of Prograf used in other solid organ transplant settings provided confirmatory evidence of effectiveness."[12] As the Agency explained when announcing the decision, "This approval reflects how a well-designed, non-interventional study relying on fit-for-purpose [RWD], when compared with a suitable control, can be considered adequate and well-controlled under FDA regulations."[13] Another recent example is FDA's approval of Orencia® (abatacept), with a registry-based clinical study providing additional evidence of effectiveness.[14]

We applaud FDA for highlighting these approvals as examples in which RWE has been used successfully in regulatory decision-making and for sharing information about each use case with the public, which facilitates greater understanding of how RWD/E can be used for regulatory purposes. The final guidance should reflect FDA's approach in these approvals by explicitly confirming and clarifying that RWE can provide or help establish substantial evidence of effectiveness.

III. Transparency Regarding Data Collection and Analysis

The Draft Guidance recommends that sponsors "document all analyses performed on the data during the study design phase, including feasibility evaluations and exploratory analyses."[15] We suggest that FDA clarify the scope of this recommendation, particularly in terms of when the "study design phase"—including for exploratory analyses—begins and ends. For example, the Draft Guidance does not indicate if the study design phase occurs prior to protocol development. We recommend FDA enhance this discussion in the final guidance by acknowledging that the scope is study-specific and that, generally, there is a key distinction between conducting early analyses to identify whether the data are fit-for-purpose and testing a study hypothesis. At a minimum, feasibility analyses that do not involve hypothesis testing—that is, assessing the causal relationship between an exposure variable and an outcome variable—should be considered to fall

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for Evaluating Marketed Product Effectiveness (Dec. 19, 2019), https://healthpolicy.duke.edu/sites/default/files/2020-08/Totality%20of%20Evidence%20Approach.pdf.

[12] FDA, *FDA Approves New Use of Transplant Drug Based on Real-World Evidence* (July 2021), https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence.

[13] *Id.*

[14] FDA, *FDA Approves First Drug to Prevent Graft Versus Host Disease* (Dec. 2021), https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-prevent-graft-versus-host-disease.

[15] Draft Guidance at Lines 164–165.

under the former (and thus outside the scope of a study design phase).[16] For these feasibility evaluations, either the statistical analysis plan or the data management plan should provide information regarding how the inclusion/exclusion criteria were selected and how the data were transformed.

The Draft Guidance also recommends that sponsors "describe in the study protocol all the data sources accessed when designing the study, as well as results from feasibility evaluations or exploratory analyses of those data sources."[17] As with the documentation recommendation above, we encourage FDA to provide more detail as to the scope of these recommendations, particularly with regard to when this recommendation begins and ends, as well as to differentiate the Agency's recommendations for feasibility evaluations. Additionally, a "data source" may be used by different sponsors and for different development programs, and over time a data source may be further curated by an RWD/E organization. Presumably FDA's recommendation is focused on the specific time period for each particular study of a drug or biological product and "evaluations and exploratory analyses of those data sources" performed to design this relevant study, but clarifying the scope of FDA's recommendation would be helpful.

This section of the Draft Guidance also recommends that sponsors post study protocols on a publicly available website "[t]o ensure transparency regarding their study design."[18] We agree with the importance of transparency about study designs to promote trust in RWE studies. As a general matter, study protocols should be published in accordance with the requirements for ClinicalTrials.gov, and we recommend that FDA update its recommendation so that it aligns with these existing requirements and encourages registration on the Real-World Evidence Transparency Initiative's recently launched Real World Evidence Registry.[19] To the extent FDA contemplates the voluntary disclosure of protocols beyond what is already required, the Agency should acknowledge in the final guidance that such publication would be voluntary.

IV. Safety Reporting

We appreciate FDA's attention to safety reporting obligations in the Draft Guidance. To enhance the discussion in the final guidance, we recommend that FDA highlight the distinctions that can exist between adverse event reporting during a non-interventional retrospective RWE study and reporting in the routine postmarketing context. The former involves the secondary use of data, such as RWD collected from EHRs or patient medical records. The manner in which these data are extracted often involves a combination of methodologies (e.g., a combination of human abstraction, machine learning, or other programmatic methods) that may make it difficult to clearly determine

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[16] Berger ML et al., *Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making*, Value in Health 20 (2017) 1003–1008.

[17] Draft Guidance at Lines 157–159.

[18] *Id.* at Lines 174–177.

[19] *See* https://osf.io/registries/rwe/discover.

facts for analyzing and interpreting individual case safety reports. Unlike in the routine postmarketing context, it will generally not be possible to conduct follow-up during an RWE study to obtain additional information about an adverse event. This data collection from RWD sources such as EHRs could result in reports with little or no relationship to the drug being studied and minimal utility for promoting patient safety.

For these reasons, we ask FDA to define in the final guidance the appropriate scope of adverse events to be reported from non-interventional retrospective RWE studies. We suggest that an adverse event should be considered reportable for these studies only if there is a reasonable possibility, based on the information available in the patient's record,[20] that the drug of interest caused the adverse event. Applying this proposed standard would parallel FDA's safety reporting requirements for postmarketing studies and other organized data collections[21] and be consistent with the approach taken in other jurisdictions for non-interventional studies, which have distinguished safety reporting for non-interventional postmarketing studies involving secondary use of data. For example, under its guidelines for the secondary use of data in non-interventional studies, the European Medicines Agency does not require the submission of individual case safety reports and instead expects that "[a]ll adverse events/reactions . . . be recorded and summarised in the interim safety analysis and in the final study report."[22]

We also ask FDA to clarify the statement that "[a]pplicants of NDAs and BLAs *and other responsible parties* are subject to regulatory requirements regarding postmarketing safety reporting."[23] The italicized text could cause confusion about who FDA considers to be "other responsible parties" subject to regulatory requirements. We understand the italicized text to be referring to "any person other than the applicant whose name appears on the label of an approved drug product as a manufacturer, packer, or

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[20] We agree with the Draft Guidance that a sponsor should not be expected to search the larger real-world dataset in order to identify adverse events because they often use only a "subset" of this larger dataset to conduct analyses. For the same reason, we suggest FDA clarify that only information in the "subset" of the patient's record used in an RWE study should trigger a safety reporting obligation if the information in the rest of the record is not reviewed.

[21] *See* 21 C.F.R. §§ 314.80(e), 600.80(e).

[22] EMA, *Guideline on Good Pharmacovigilance Practices (GVP): Module VI—Collection, Management, and Submission of Reports of Suspected Adverse Reactions to Medicinal Products*, EMA/873138/2011 Rev 2 (July 28, 2017), https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf. *See also* International Society for Pharmacoepidemiology, *Guidelines for Good Pharmacoepidemiology Practices* (June 2015), https://www.pharmacoepi.org/resources/policies/guidelines-08027/ (distinguishing between primary data collection studies and studies using secondary data sources for adverse event reporting in pharmacoepidemiology studies and noting that, for the latter, "[t]hese studies are generally required to report adverse drug reactions documented in the medical record/narrative text only").

[23] Draft Guidance at Lines 215–216.

distributor (nonapplicant)," consistent with the Agency's safety reporting regulations.[24] FDA should confirm this meaning in the final guidance.[25]

V. Applicability of Part 11

The Draft Guidance states that "the electronic systems used by the sponsor to manage the data and produce required records" for a marketing application containing a non-interventional study "must comply with 21 CFR part 11."[26] We ask the Agency to clarify the extent to which part 11 applies in this context in two regards.

First, we would appreciate clarity on whether part 11 applies to tools used to conduct analyses on RWD (e.g., analytics platforms) and if FDA expects source data providers to ensure their systems comply with part 11. We note FDA has previously stated that the Agency "does not intend to assess the compliance of EHRs with part 11."[27] If FDA does expect such compliance for all systems used to manage data (other than EHRs), we would appreciate guidance on how FDA envisions compliance, as a large variety of data sources and organizations could provide useful RWD/E for regulatory decision-making.

Second, we appreciate that footnote 19 of the Draft Guidance cross-references two separate draft guidances regarding part 11 compliance. It is not readily apparent, however, if FDA means to imply that the entirety of these other guidances apply in this context. For example, the draft guidance entitled "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11—Questions and Answers" ("Part 11 Q&A Draft Guidance") distinguishes between electronic services that are outsourced and those handled in-house. It is not clear to what extent FDA intends to apply that distinction in the RWD/E context. Similarly, the Part 11 Q&A Draft Guidance also states that FDA does not intend to assess the compliance of electronic systems used in the provision of medical care, such as EHRs, with part 11. We ask FDA to clarify that the aspects of part 11 currently subject to FDA's enforcement discretion will likewise be subject to enforcement discretion in the RWD/E context.

VI. RWD Data Access

The Alliance fully supports the concept of data provenance and the need for transparency in the conduct and submission of studies utilizing RWD that will facilitate FDA's analysis of the data. In the Draft Guidance, FDA recommends that sponsors ensure that "source data necessary to verify the RWD" are made available for

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[24] 21 C.F.R. § 314.80(c)(1)(iii).

[25] We recognize that sponsors may transfer responsibility for any of its obligations under part 312 to a third party, consistent with 21 C.F.R. § 312.52, but understand this passage in the Draft Guidance to be referring to parties that are subject to FDA's postmarketing safety reporting regulation.

[26] Draft Guidance at Lines 235–238.

[27] FDA, *Guidance for Industry: Electronic Source Data in Clinical Investigations* 8 (Sept. 2013), https://www.fda.gov/media/85183/download.

inspection.[28] Per the Draft Guidance, source data include information in original records.[29] In some cases, however, the sponsor and RWD/E organization may not have the ability to provide full access to original source records due to certain constraints. For example, limitations may arise if these records contain identifiable, patient-specific information subject to certain restrictions; if third parties limit access to the entity's databases (but nevertheless have useful RWD to guide FDA's regulatory decision-making); if the data are sourced from an ex-U.S. jurisdiction that does not permit data to leave the country's borders; or if the analyses are run at local sites so the sponsor and/or contract research organization receives only aggregate results. In these contexts, we recommend that the Agency consider alternatives to reviewing source data that will provide FDA with suitable confidence regarding the information that has been submitted. For example, RWD/E organizations could provide information regarding their quality processes that help ensure robust data structuring, such as the use of inter-rater reliability systems, other data quality management functions, and/or a description of the data extraction process and the quality controls in place for data collection.

In those circumstances where review of patient-level data is appropriate, we also recommend that the final guidance reflect the privacy considerations presented by the sharing of patient-level data. As an initial matter, we encourage FDA to clarify that any patient-level data submitted to FDA from an RWE study would be *de-identified*[30] patient-level data, which helps protect the privacy interests of the patients even if such data may still be protected under relevant data protection laws.[31] Data from jurisdictions outside the United States, such as from Europe, could present considerations in particular due to their privacy laws. FDA may consider remote access mechanisms (such as on-platform reviews) as an option in order to access these de-identified data without actually transferring copies of patient-level data.[32] If FDA plans to receive patient-level data, we recommend the Agency confirm that local privacy laws governing the data would apply to any access of such data by the Agency.

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[28] Draft Guidance at Lines 189–191.

[29] *Id.* at n.13. We encourage FDA to add "source data" to the glossary. We note, however, that the Draft Guidance uses a different definition for this term than in the Data Standards Draft Guidance. The Draft Guidance defines "source data" as "all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation *used for* reconstructing and evaluating the investigation." The Data Standards Draft Guidance, on the other hand, defines "source data" as "all information . . . *necessary for* the reconstruction and evaluation of the study." We recommend that FDA align the definition across RWE guidances to reflect the latter definition. This revision would facilitate implementation of the Agency's recommendations, as the difference in wording could result in different interpretations of what constitutes "source data."

[30] *See* 5 C.F.R. § 164.514(b)(1) (HIPAA expert determination method for de-identification).

[31] *See* Draft Guidance at Lines 183–186.

[32] Identifying these alternative approaches for reviewing data would also help address issues presented by the submission of analytic datasets to FDA, as discussed in our comments on the Data Standards Draft Guidance. *See* RWE Alliance, Comments on Docket No. FDA-2021-D-0548 2–3 (Feb. 4, 2022) ("Comments on Data Standards Draft Guidance").

Additionally, FDA states that sponsors should ensure that RWD and associated programming codes and algorithms submitted to FDA are "documented, well-annotated, and complete, which would allow FDA to replicate the study analysis using the same dataset and analytic approach."[33] We agree with the importance of allowing FDA to replicate the study analysis. But as noted in our comments on the draft guidance entitled "Data Standards for Drug and Biological Product Submissions Containing Real-World Data,"[34] any conversion of RWD to a supported standard prior to the creation of the analytic dataset would raise many of the considerations that FDA previously identified for common data models ("CDMs").[35] If FDA recommends converting data to a supported format prior to analysis, we would appreciate further guidance about applying the Agency's other recommendations for CDMs in this context.

VII. Additional Comments

The RWE Alliance offers the following additional comments and suggested clarifications on the Draft Guidance.

- We appreciate FDA's reference to clinical trials with pragmatic elements in the Draft Guidance.[36] We suggest expanding this discussion in the final guidance to improve stakeholder understanding of this particular trial design. For example, clinical trials using pragmatic elements can help control for bias while also allowing for contemporaneous follow-up on patients in a real-world setting. We would also welcome guidance from FDA about the design of clinical trials with pragmatic elements.

- We recommend that FDA add the terms "algorithm" and "programming codes" to the glossary and, for their respective definitions, distinguish between (1) algorithms and codes used for data curation purposes (e.g., code for extraction and generation of RWD); and (2) algorithms and codes used for a specific study analysis.

VIII. Conclusion

The RWE Alliance appreciates the Agency's commitment to advancing the use of RWD and RWE in regulatory decision-making. Thank you for considering these comments,

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[33] Draft Guidance at Lines 193–195.

[34] Comments on Data Standards Draft Guidance at 7.

[35] *See* FDA, *Draft Guidance for Industry: Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* 8–9 (Sept. 2021) (noting, for example, that data in CDM-driven networks "rarely contain all of the source information present at the individual healthcare sites").

[36] *See* Draft Guidance at Lines 62–64.

and please let us know if you have any questions. We would welcome the opportunity to discuss further.

Best regards,

The RWE Alliance