REAL-WORLD EVIDENCE ALLIANCE

info@rwealliance.org
rwealliance.org

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Office of Science Policy
National Institutes of Health (NIH)
6705 Rockledge Drive, Suite 630
Bethesda, MD 20892

Re: Request for Information: FDA-NIH Resource on Terminology for Clinical Research (Notice No. NOT-OD-24-112)

To FDA and the NIH Office of Science Policy:

The RWE Alliance appreciates the opportunity to comment on the Request for Information titled "FDA-NIH Resource on Terminology for Clinical Research" (the "RFI")[1] and its corresponding document titled "FDA-NIH Terminology for Clinical Research: Glossary of Terms and Definitions (the "Glossary"). 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 the lives of patients. 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 from electronic health records, administrative claims and billing records, product and disease registries, personal devices, wearables, and health applications will be used to generate evidence to support regulatory decision making related to medical product safety and effectiveness. To achieve these goals, 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, (4) increase communication on the generation and use of RWE, and (5) recognize the unique aspects of and opportunities for RWD/E.[3]

We applaud FDA and NIH for releasing a Glossary to promote consistency in the use of clinical research terms related to innovative clinical study designs, including studies

[1] Notice No. NOT-OD-24-112 (May 6, 2024).

[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/.

involving RWD. The use of a common vocabulary will help the RWE ecosystem to characterize clinical research and communicate with regulators and other stakeholders about study design and research results. We encourage the FDA and NIH working group to continue to engage with the RWE ecosystem to align on clinical research terminology.

Section I of this letter provides comments on the clinical research terms that are included in the Glossary and for which FDA and NIH are seeking comments (referred to as "terms included for comment" by FDA and NIH). Section II provides comments on other terms that the RWE Alliance proposes to include in the Glossary (referred to as "other pertinent terms that are inconsistently used within the scientific community" by FDA and NIH).

I. Comments on the Terms Included for Comment

The following table outlines the RWE Alliance's commentary on and proposed revisions to the Glossary's terms included for comment. For ease of reference, we list terms below in alphabetical order.

Term	Commentary	Current Glossary Definition	Proposed Revisions
Administrative Claims Data	We recommend clarifying the abbreviation related to "ICD" by incorporating either one of the two proposed revisions.	"The information obtained from claims that health care providers submit to insurers to receive payment for treatments and other interventions. Claims data use standardized medical coding systems (nomenclatures), such as the World Health Organization International Classification of Diseases Coding (ICD-CM) to identify diagnoses, National Drug Code (NDC) to identify drugs, and Current Procedural Terminology (CPT®) to identify procedures."	Option 1: "The information obtained from claims that health care providers submit to insurers to receive payment for treatments and other interventions. Claims data use standardized medical coding systems (nomenclatures), such as the World Health Organization International Classification of Diseases ~~Coding~~, Clinical Modification (ICD-CM) to identify diagnoses, National Drug Code (NDC) to identify drugs, and Current Procedural Terminology (CPT®) to identify procedures." Option 2: "The information obtained from claims that health care providers

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			submit to insurers to receive payment for treatments and other interventions. Claims data use standardized medical coding systems (nomenclatures), such as the World Health Organization International Classification of Diseases ~~Coding~~ (ICD-~~CM~~) to identify diagnoses, National Drug Code (NDC) to identify drugs, and Current Procedural Terminology (CPT®) to identify procedures."
Causal Effect	We suggest removing reference to "measure of difference" because a causal effect is not itself a measure of difference, but instead a comparison of the distribution of the outcome, and the term "difference" might be confused with absolute versus relative measures. In addition, we recommend that the Glossary clarify that its definition is referring to a population causal effect as opposed to an individual causal effect.	"Causal Effect: A measure of difference in outcome that would be expected in individuals subjected to an exposure of interest compared to the expected outcome if those same individuals were subjected to a specified alternative exposure (including no exposure)."	"Causal Effect (Population-level): A ~~measure of difference in~~ comparison of the distribution of the outcome ~~that would be expected~~ in a population if all individuals were subjected to an exposure of interest compared ~~to the expected~~ with the distribution of the outcome if ~~those~~ these same individuals were subjected to a specified alternative exposure (including no exposure)."

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Common Data Model (CDM)	We believe that the definition of CDM can be strengthened by referencing its purpose, i.e., to harmonize across various data sources. The current Glossary definition is unclear, particularly with the use of the word "interoperability," and may be difficult to interpret.	"Comprehensive framework that includes definitions, specifications, and operational rules for data to be presented and used in a common manner to enable interoperability."	"A comprehensive framework for organizing data that includes definitions, specifications, and operational rules ~~for~~ to ensure data ~~to be~~ from different sources are presented and used in a common manner ~~to enable interoperability~~."
Confounding	We believe that the Glossary definition reflects an older version of the concept of "confounding" and would benefit from an update to reflect currently accepted practice in epidemiology.	"Systematic error in estimation of the measure of the effect of a medical product on an outcome due to another factor that is associated with both the exposure and the outcome and not through the causal pathway between exposure and outcome."	"A systematic ~~error in estimation of the measure of the effect of a medical product on an outcome due to another factor that is associated with both~~ difference between the estimated and true effects attributable to the presence of common causes of the exposure and ~~the~~ outcome ~~and not through the causal pathway between exposure and outcome~~ of interest."
Data Curation	We believe this definition would be strengthened and clarified by using a definition similar to the definition in FDA's draft guidance titled "Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-	"Processing of source data (unstructured and/or structured data) into a dataset suitable for analyses. The curation process involves the application of standards for the exchange, integration, sharing, and retrieval of source data, often from various sources. For example, the	"~~Processing of source data (unstructured and/or structured data) into a dataset suitable for analyses. The curation process involves the application of standards for the exchange, integration, sharing, and retrieval of source data, often from various sources.~~ Application of

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	Making for Drug and Biological Products."	application of standard medical diagnostic codes to adverse events, disease staging, the progression of disease, and other medical and clinical concepts."	standards (e.g., Health Level 7, ICD-10-CM) to source data; ~~F~~for example, the application of ~~standard medical diagnostic~~ codes to adverse events, disease staging, the progression of disease, and other medical and clinical concepts in an electronic health record (EHR) system."
Data Lake	We suggest the proposed revision.	"A controlled, centralized environment that stores structured and unstructured data in its native form and provides infrastructure for organizing large volumes of diverse data from multiple sources."	"A ~~controlled~~ secure, centralized environment that stores structured and unstructured data in its native form and provides infrastructure for organizing large volumes of diverse data from multiple sources."
Information Bias	We believe that the Glossary definition could be more precise, including by noting that measurement error in a continuous variable can result in misclassification.	"Systematic error in estimation of an association or other parameter of interest arising from measurement error in the data. For categorical variables, measurement error is usually called classification error or misclassification."	"A systematic ~~error in estimation of an association or other parameter of interest arising from measurement error in the data. For categorical variables, measurement error is usually called~~ difference between the estimated and true effects attributable to error in the measurement of variables (e.g., exposure, outcome, and covariates). This measurement error is sometimes referred to as classification error or misclassification."

Term	Commentary	Current Glossary Definition	Proposed Revisions
Interventional Study	We believe that the Glossary definition should be simplified to refer to protocol-required assessments without reference to study objectives.	"A study involving participants (e.g., healthy individuals or individuals with a disease or condition of interest) whose exposure or interaction with a medical product is assigned according to a study protocol to evaluate the effect on health outcomes or product performance."	"A study involving participants (e.g., healthy individuals or individuals with a disease or condition of interest) whose ~~exposure or interaction~~ exposure/interaction with a medical product is assigned according to a study protocol ~~to evaluate the effect on health outcomes or product performance~~."
Observational Study, Retrospective	FDA's draft guidance titled "Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products" states: "[T]he terms *prospective* and *retrospective* are commonly but variably used to indicate whether timing of the cause-effect association occurs prior to or concurrent with the investigation that is examining it, whether inferential reasoning is from cause-to-effect or vice versa, whether sample selection is based on exposure or outcome status, or whether a study hypothesis is established prior to or after the corresponding data were collected."	"A study that identifies the population and determines the exposure/treatment from data collected before the initiation of the study. The variables and outcomes of interest are determined at the time the study is designed."	"~~A study that identifies the population and determines the exposure/treatment from data collected before the initiation of the study. The variables and outcomes of interest are determined at the time the study is designed.~~ Secondary Data Collection Study: A study in which data are obtained from an existing data source where data were collected for a purpose other than the specific study at hand, and study follow up does not necessarily coincide with real time. Examples include administrative claims databases, electronic health records databases, completed clinical trials, and existing registries."

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	To align with the draft guidance, we recommend removing the term "Observational Study, Retrospective" from the Glossary and replacing it with "Secondary Data Collection Study."		
Observational Study, Prospective[4]	For the same reason, we recommend removing the term "Observational Study, Prospective" from the Glossary's "Terms for Reference" in Appendix A and replacing it with "Primary Data Collection Study."	"A study in which the population of interest is identified at the start of the study, and exposure/treatment and outcome data are collected from that point forward. The start of the study is defined as the time the research protocol for the specific study question was initiated."	"Primary Data Collection Study: A study ~~in which the population of interest is identified at the start of the study, and exposure/treatment and outcome data are collected from that point forward. The start of the study is defined as the time the research protocol for the specific study question was initiated~~ with *de novo* data collection (i.e., directly from clinical sites, patients, or health care providers) for the purposes of the study at hand."
Registry	Because a registry may be initiated de novo to address a particular research question or an existing registry may be leveraged to address several research questions, data fitness	"An organized system that collects clinical and other data in a standardized format for a population defined by a particular disease, condition, or exposure."	"An organized system that collects clinical and other data in a standardized format for a population defined by a particular disease, condition, or exposure. A registry may be built for the purpose of

[4] We recognize that FDA and NIH are not seeking comment on this term. However, we believe that it is important to align this term with FDA's draft guidance, "Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products," and thus offer our comments for consideration.

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	considerations should be tailored accordingly. We propose a revision to emphasize this point.		a particular research question/study, or it may be used to address multiple research questions identified after registry initiation."
Selection Bias	We find that definitions of selection bias are often unclear because they are not sufficiently distinguished from confounding and seek to cover both internal and external validity. We suggest modifying the Glossary definition to focus on internal validity.	"Systematic error in estimation of an association or other parameter that occurs from factors that influence study participation [or eligibility]."	"A systematic ~~error in estimation of an association or other parameter~~ difference between the estimated and true effects for the study-eligible population that occurs ~~from factors that influence study participation [or eligibility]~~ when the outcome and exposure of interest are associated with factors that determine inclusion in the final analytic population."
Synthetic Data	We believe that this definition would be strengthened by modifying the last clause to remove the reference to "real" information, which implies a negative connotation about the usefulness of such data.	"Data that have been created artificially (e.g., through statistical modeling, computer simulation) so that new values and/or data elements are generated. Generally, synthetic data are intended to represent the structure, properties and relationships seen in actual patient data, except that they do not contain any real or specific information about individuals."	"Data that have been created artificially (e.g., through statistical modeling, computer simulation) so that new values and/or data elements are generated. Generally, synthetic data are intended to represent the structure, properties and relationships seen in actual patient data, except that they do not contain any ~~real or specific information about individuals~~ individually identifiable information."

Term	Commentary	Current Glossary Definition	Proposed Revisions
Target Trial Emulation	We suggest adding a citation to this definition.	"A framework for designing and analyzing an observational study based on conceptualizing a target randomized trial to answer a scientific question and designing the observational study to mimic the trial estimand(s) (including specification of population eligibility criteria, treatment strategies and assignment procedures, outcomes, handling of intercurrent events, and follow-up period)."	Add: "*Source*: Hernán MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. JAMA. 2022;328(24):2446–2447. doi:10.1001/jama.2022.21383."

III. Comments on Other Pertinent Terms Used Inconsistently Within the Scientific Community

The following table outlines the RWE Alliance's commentary on and proposed definitions for other pertinent terms used inconsistently within the scientific community.

Term	Commentary	Proposed Definition
Estimand	We believe that the term "estimand" is often confused with other epidemiological concepts and would thus benefit from a definition aligned with FDA guidance, "E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials" Rev. 1 (2021).[5]	"A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared."

[5] https://www.fda.gov/media/148473/download.

Term	Commentary	Proposed Definition
Externally Controlled Trial	We find that the term "externally controlled trial" is subject to wide interpretation and varied meaning in practice. This is especially true when considering the subsets of externally controlled trials, such as external control benchmarks versus external control arms. Often, the latter term is used interchangeably with "synthetic control arms," creating confusion regarding the data source used.	"An externally controlled trial is a clinical investigation where outcomes in participants receiving the test treatment according to a protocol are compared to outcomes in a group of people external to the trial who had not received the same treatment."[6]
External Control Arm	For the same reason, we recommend defining the term "external control arm."	"An external control arm is a cohort of control patients that are collected from data external to a single-arm trial. To provide an unbiased estimation of efficacy, the clinical profiles of patients from the single-arm trial and external control arm should be aligned, typically using matching methods (e.g. propensity score approaches)."[7]
External Control Benchmark	For the same reason, we recommend defining the term "external control benchmark."	"An external control benchmark is an estimated outcome rate from patients without the treatment of interest that is compared with the outcome rate observed in patients receiving the treatment of interest through a clinical trial, with no

[6] FDA, Draft Guidance, Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (2023).

[7] Loiseau N, Trichelair P, He M et al. External Control Arm Analysis: An Evaluation of Propensity Score Approaches, G-computation, and Doubly Debiased Machine Learning. BMC Med Res Methodol. 2022;22(1):335. https://doi.org/10.1186/s12874-022-01799-z.

Term	Commentary	Proposed Definition
		confounding control (e.g., age-matching) applied.”

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Thank you for your leadership on promoting consistent terminology related to studies involving RWD and facilitating better communication within the RWE ecosystem and with the broader clinical research community. We appreciate your consideration of our feedback on the Glossary. Please let us know if you have any questions. We welcome the opportunity to discuss further.

Best regards,

The RWE Alliance