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# Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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## Draft Guidance for Industry and Food and Drug Administration Staff

***DRAFT GUIDANCE***

**This draft guidance document is being distributed for comment purposes only.**

**Document issued on December 19, 2023.**

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact the Office of Clinical Evidence and Analysis at [CDRHClinicalEvidence@fda.hhs.gov](mailto:CDRHClinicalEvidence@fda.hhs.gov). For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov).

**When final, this guidance will supersede “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices,” issued August 2017.**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Devices and Radiological Health  
Center for Biologics Evaluation and Research

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## **Preface**

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DRAFT

# Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

## Draft Guidance for Industry and Food and Drug Administration Staff

*This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 or Office responsible for this guidance as listed on the title page.*

### I. Introduction

FDA is issuing this draft guidance to clarify how FDA evaluates real-world data to determine whether they are of sufficient quality for generating real-world evidence that can be used in FDA regulatory decision-making for medical devices. This draft guidance also provides expanded recommendations to sponsors considering using real-world evidence to support a regulatory submission for medical devices.<sup>1</sup>

**Real-world data (RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Examples of RWD sources include data derived from electronic health records (EHRs),<sup>2</sup> medical claims data, data from product and disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status. RWD sources can be used as data

<sup>1</sup> For more information on regulatory submissions for medical devices, see Sections III. and VII.

<sup>2</sup> For the purposes of this draft guidance, an “EHR” is an electronic record of health-related information on an individual that conforms to nationally recognized/utilized interoperability standards and that can be created, managed, and consulted by authorized clinicians and staff across more than one health care organization. Definition adapted from The National Alliance for Health Information Technology Report to the Office of the National Coordinator for Health Information Technology on Defining Key Health Information Technology Terms April 28, 2008, available at [webarchive.library.unt.edu/eot2008/20080920183033/http://www.hhs.gov/healthit/documents/m20080603/10\\_2\\_hit\\_terms.pdf](http://webarchive.library.unt.edu/eot2008/20080920183033/http://www.hhs.gov/healthit/documents/m20080603/10_2_hit_terms.pdf)

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28 collection and analysis infrastructure to support many types of study designs, including, but not  
29 limited to, randomized and non-randomized controlled trials; single-arm studies with or without  
30 comparison to an objective performance criterion, performance goal, or extended control;  
31 observational studies; and hybrid designs which combine elements of multiple study designs.

32  
33 **Real-world evidence (RWE)** is the clinical evidence regarding the usage, and potential benefits  
34 or risks, of a medical product derived from analysis of RWD.

35  
36 This draft guidance includes factors that FDA considers important to demonstrate whether the  
37 RWD are fit-for-purpose for a particular regulatory decision relating to medical devices, as well  
38 as FDA’s recommendations on how FDA intends to assess these factors. When finalized, the  
39 recommendations and considerations in this draft guidance will apply regardless of the RWD  
40 source and encompass processes for conducting studies to generate RWE. A fit-for-purpose  
41 assessment should evaluate both the relevance and reliability of the RWD, discussed in more  
42 detail in Section V. FDA recognizes that there may be other approaches to address the  
43 considerations identified in this document. We encourage sponsors to discuss their approach with  
44 FDA, especially if the approach diverges from the recommendations in this draft guidance, when  
45 finalized.<sup>3</sup>

46  
47 FDA recognizes and anticipates that the Agency and industry may need up to 60 days to perform  
48 activities to operationalize the recommendations within the final guidance. At this time, the  
49 Agency anticipates that, for regulatory submissions that will be currently pending with FDA after  
50 publication of the final guidance, as well as those submissions received within 60 days following  
51 publication of the final guidance, FDA generally would not anticipate that sponsors will be ready  
52 to include the newly recommended information outlined in the final guidance in their  
53 submission. FDA, however, would intend to review any such information if submitted at any  
54 time.

55  
56 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
57 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
58 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
59 the word *should* in Agency guidances means that something is suggested or recommended, but  
60 not required.

61

## 62 **II. Background**

63 To protect and promote public health, FDA needs to understand and evaluate the available  
64 evidence related to regulated products. For medical devices, common sources of available  
65 evidence include non-clinical and clinical studies<sup>4</sup> provided to FDA by a device manufacturer or

---

<sup>3</sup> See FDA’s guidance, “Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program>

<sup>4</sup> For the purposes of this draft guidance, we use the term “clinical studies” in this guidance as a broad term to capture clinical research regarding the safety or effectiveness of a device, regardless of study design. We use the term “traditional clinical studies” to refer to clinical studies that do not utilize RWD.

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66 sponsor of a device premarket or postmarket submission. FDA recognizes that a wealth of  
67 clinical data in the form of RWD are routinely collected in the course of clinical practice during  
68 the treatment and management of patients. Although these data typically have different quality  
69 controls compared to data collected within a traditional clinical study, under certain  
70 circumstances RWD may be used to generate RWE to help inform or augment FDA’s  
71 understanding of the benefit-risk profile of devices at various points in their life cycle. Per 21  
72 CFR 860.7(c)(1), “[a]lthough [a] manufacturer may submit any form of evidence to the Food and  
73 Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the  
74 agency relies upon only valid scientific evidence to determine whether there is reasonable  
75 assurance that the device is safe and effective.” RWE derived from relevant and reliable RWD  
76 may constitute valid scientific evidence,<sup>5</sup> depending on the study question, regulatory decision,  
77 data source(s), and design and analysis of the specific dataset derived from RWD source(s), and  
78 thus may be used to support regulatory decisions. FDA intends to use the considerations  
79 described in this draft guidance, when finalized, to evaluate whether RWD are relevant and  
80 reliable to support regulatory decision-making, including potentially generating valid scientific  
81 evidence. The use of RWE for specific regulatory purposes will include assessment of the overall  
82 relevance and reliability of the RWD used to generate the RWE.

83  
84 When appropriate, use of RWD may provide an efficient means of generating the necessary  
85 clinical evidence to support regulatory decisions. Information specific to the clinical performance  
86 of a device can be generated through a number of methodological and operational approaches. In  
87 general, traditional clinical studies tend to be narrow in scope but allow for more control of  
88 sources of error and bias. In comparison, studies that leverage RWD may be able to evaluate  
89 broader questions but are subject to sources of bias which may be more difficult to control.  
90 Clinical evidence can be generated from studies using RWD, alone or in combination with data  
91 from more traditional clinical studies. Using appropriate design and methodologies, sponsors can  
92 leverage the strengths of these approaches while minimizing potential weaknesses.

93  
94 RWD that includes patient experience data<sup>6</sup> may provide new insights into the performance of a  
95 device. In addition, RWD may foster inclusion of target populations that are otherwise  
96 underrepresented in clinical studies. Similarly, leveraging RWD may allow for studies of a  
97 longer period of time than would be practical in a traditional clinical study and so may allow for  
98 data to be gathered on longer term outcomes. Clinical evidence generated from fit-for-purpose

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<sup>5</sup> Under 21 CFR 860.7(c)(2), “valid scientific evidence” is considered “evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.”

<sup>6</sup> For the purposes of this draft guidance, “patient experience data” means data that are (1) collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and (2) are intended to provide information about patients’ experiences with a disease or condition, including (A) the impact of such disease or condition, or a related therapy, on patients’ lives; and (B) patient preferences with respect to treatment of such disease or condition. *See* section 3001 of the 21st Century Cures Act, Pub. L. No. 114-255 (December 2016).

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99 RWD informs device benefit-risk profiles assessment from a real-world environment, allows  
100 evaluation of outcomes which may not be feasible in traditional clinical studies, and better aligns  
101 with device innovation cycles to inform future device modifications and new technology  
102 development. Finally, RWD may include information from broader clinical experiences than is  
103 usually represented in traditional clinical studies. RWE is an important factor for understanding  
104 and regulating medical devices, and therefore, FDA encourages the medical community to learn  
105 more from routine clinical care to help support safety and effectiveness of medical devices. Use  
106 of relevant and reliable RWD to generate RWE can benefit stakeholders throughout the  
107 ecosystem, including but not limited to, patients, health care providers, manufacturers, and FDA.  
108

109 Additionally, in some cases, a traditional clinical study may be impractical or excessively  
110 challenging to conduct. Ethical issues regarding treatment assignment, and other similar  
111 challenges, may present themselves when developing and attempting to execute such a study.  
112 Analyses of RWD, using appropriate methods, may in some cases provide similar information  
113 with comparable or even superior characteristics to information collected and analyzed through a  
114 traditional clinical study. Under the right conditions, RWE may be suitable to support the  
115 marketing authorization of a new device or the expansion of the indications for use of devices  
116 that are already on the market. Aggregation of RWD (e.g., in a medical device registry<sup>7</sup>) may  
117 prove useful as a postmarket control suitable for providing ongoing device safety surveillance  
118 and additional evidence for effectiveness. FDA has long applied postmarket controls as a way to  
119 reduce premarket data collection, while still ensuring that the statutory standard of reasonable  
120 assurance of safety and effectiveness is met.<sup>8</sup> FDA believes that applying postmarket controls to  
121 reduce premarket data collection, when appropriate, can help improve patient access to safe and  
122 effective medical devices.<sup>9</sup>  
123

124 Many of the considerations and best practices for generating RWE are derived from the same  
125 principles that govern generation of clinical evidence from traditional clinical studies, which are  
126 generally referred to as good clinical practice (GCP). Additionally, as with all clinical evidence  
127 FDA evaluates, FDA's assessment of RWE evaluated in support of a particular regulatory  
128 decision will be included as part of the totality of information available to FDA. Further, as with  
129 all types of clinical data, FDA recognizes there may be uncertainty of the benefits and risks of a  
130 device that remain after completion of a study using RWD. Some of these aspects are similar to  
131 those also present in more traditional forms of clinical data, but some are unique to RWD.

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<sup>7</sup> For the purposes of this draft guidance, “medical device registry” means an organized system with a primary aim to increase the knowledge on medical devices contributing to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g., international, national, regional, and health system). Definition is cited from the IMDRF document “Principles of International System of Registries Linked to Other Data Sources and Tools,” available at <https://www.imdrf.org/documents/principles-international-system-registries-linked-other-data-sources-and-tools>

<sup>8</sup> For more information, see FDA's guidance “The Least Burdensome Provisions: Concept and Principles,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles>

<sup>9</sup> For more information, see FDA's guidance “Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval>

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132 Assessment of the relevance and reliability of the RWD, as outlined in this draft guidance, can  
133 identify uncertainty that should be considered during the benefit-risk determinations<sup>10</sup> for the  
134 device for a given regulatory purpose.  
135

136 In 2017, FDA issued the guidance document, [Use of Real-World Evidence to Support](#)  
137 [Regulatory Decision-Making for Medical Devices](#),<sup>11</sup> in which we described the relevance and  
138 reliability factors of RWD that FDA assesses to determine if RWD are sufficient for generating  
139 RWE. Subsequently, on December 29, 2022, the Food and Drug Omnibus Reform Act of 2022  
140 (“FDORA”) was signed into law as part of the Consolidated Appropriations Act, 2023, Pub. L.  
141 No. 117-328. Section 3629 of FDORA “Facilitating the Use of Real World Evidence” directs  
142 FDA to issue or revise existing guidance on considerations for the use of RWD and RWE to  
143 support regulatory decision-making. FDA is issuing this draft guidance to propose revisions to  
144 the 2017 guidance, [Use of Real-World Evidence to Support Regulatory Decision-Making for](#)  
145 [Medical Devices](#), to satisfy the requirement under section 3629(a)(2). This draft guidance also  
146 fulfills a commitment in Section V.F. of the Medical Device User Fee Amendments Performance  
147 Goals and Procedures, Fiscal Years 2023 Through 2027 (MDUFA V).<sup>12</sup> This draft guidance is  
148 intended to provide expanded and updated recommendations to industry and FDA staff for  
149 conducting an assessment of relevance and reliability to demonstrate that RWD may be fit-for-  
150 purpose to generate clinical evidence for regulatory decision-making. This includes  
151 recommendations to provide clarity on least burdensome general expectations related to  
152 demonstrating that RWD is fit-for-purpose for premarket regulatory purposes.  
153

### 154 **III. Scope**

155 This draft guidance is applicable for the use of RWE to support regulatory submissions for  
156 medical devices.<sup>13</sup>  
157

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<sup>10</sup> See FDA’s guidances, “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de>; “Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de>; “Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k>; and “Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-regarding-benefit-risk-medical-device-product-availability-compliance-and>

<sup>11</sup> Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices>

<sup>12</sup> Available at <https://www.fda.gov/media/158308/download>

<sup>13</sup> This guidance does not apply to drugs and biological products. For information on the RWE program for drugs and biological products, see <https://www.fda.gov/science-research/real-world-evidence/center-biologics-evaluation-and-research-center-drug-evaluation-and-research-real-world-evidence>

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158 The topics covered within this draft guidance are framed specifically for the use of RWD and  
159 RWE in regulatory submissions for medical devices (e.g., Investigational Device Exemption  
160 (IDE), premarket notification under section 510(k) of the FD&C Act, Premarket Approval  
161 Application (PMA), Humanitarian Device Exemption (HDE), De Novo classification request,  
162 post-approval study, postmarket surveillance under Section 522 of the FD&C Act (522  
163 submissions), Clinical Laboratory Improvement Amendments (CLIA) Waiver by Applications  
164 (CW), Dual De Novo/510(k) and CLIA Waiver by Application Submissions (Duals)). The  
165 considerations included in this draft guidance may be applicable to supporting uses of RWD  
166 across the medical device total product life cycle (TPLC).

167  
168 This draft guidance does not address the use of non-clinical data, adverse event reports,  
169 secondary use of clinical study data, or systematic literature reviews. Nor does it address all  
170 possible study design/conduct or analytical methodologies. While it does describe the factors that  
171 FDA considers when evaluating relevance and reliability of RWD, it does not provide a specific  
172 set of criteria or other scoring tools for determining the suitability of any specific RWD source  
173 for generating RWE for a particular regulatory decision.

174  
175 This guidance, when finalized, should not be construed to alter or change in any way the existing  
176 evidentiary standards applicable to FDA’s regulatory decision-making. Rather, this guidance  
177 describes the circumstances under which clinical evidence generated from RWD may be used to  
178 support a variety of FDA decisions based on the existing evidentiary standards. While FDA  
179 encourages the use of relevant and reliable data to generate clinical evidence, including RWE,  
180 this draft guidance neither mandates use of RWD and RWE nor restricts other means of  
181 providing evidence to support regulatory decision-making. This draft guidance does not affect  
182 any federal, state, or local laws or regulations, or foreign laws or regulations that may be  
183 applicable to the use or collection of RWD, or that provide protections for human subjects  
184 (including informed consent requirements) or patient privacy. When finalized, this guidance  
185 should be used to complement, but not supersede, other device-specific and GCP and guidance  
186 documents.

## 187 188 **IV. Regulatory Context in Which Use of RWE May be** 189 **Appropriate**

### 190 **A. General considerations for the use of RWE**

191 In general, FDA considers the use of RWD to be fit-for-purpose to support generation of clinical  
192 evidence for regulatory decision-making for medical devices when we conclude that the RWD  
193 used to generate the RWE are relevant to and reliable for informing or supporting a particular  
194 regulatory decision. It is important to understand the strengths and limitations of the underlying  
195 RWD and how these qualities impact their relevance and reliability. Similarly, the context of the  
196 specific regulatory decision for which the RWE is being proposed is central to FDA’s evaluation.  
197

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198 FDA recognizes that RWE can be generated from a variety of RWD sources that are primarily  
199 intended for another purpose. For example, administrative claims data<sup>14</sup> are typically collected  
200 for purposes of billing or payment for medical care. Disease-specific RWD sources may be  
201 useful for tracking progression or outcomes of specific rare or poorly understood diseases.  
202 Treatment-specific RWD sources may have several purposes, including assessment and tracking  
203 of overall outcomes, providing assessment of hospital operations, informing performance  
204 improvement initiatives, or providing risk prediction and benchmarking data for specific  
205 therapies. The suitability of the RWD source may be determined by the factors outlined in  
206 Section V. and the availability of sufficient data to address the study question of interest.

207  
208 FDA does not endorse one type of RWD over another. Sponsors should select the appropriate  
209 RWD sources based on their suitability to address the specific study questions. Data sources that  
210 may be considered RWD sources include the following:<sup>15</sup>

- 211 • Registries;<sup>16</sup>
- 212 • EHRs;
- 213 • Administrative claims data;
- 214 • Patient-generated data<sup>17</sup> created, reported, or gathered by patients including in-home use  
215 settings (e.g., data from digital health technologies (DHTs)<sup>18</sup> such as wearables);
- 216 • Device-generated data (e.g., implantable devices, physiological monitoring devices);
- 217 • Public health surveillance data (e.g., COVID-19<sup>19</sup> case surveillance);
- 218

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<sup>14</sup> For the purposes of this draft guidance, “administrative claims data” means claims data that arise from a person’s use of the health care system and reimbursement of health care providers for that care. Definition adapted from Strom et al., *Textbook of Pharmacoepidemiology* 6<sup>th</sup> ed. 2022, page 137.

<sup>15</sup> Generally, FDA does not consider published literature to be RWD. Literature may report data from an RWD source, in which case sponsors should specify the RWD source type (e.g., if a journal article presents a retrospective analysis of EHRs, the RWD source should be specified as EHR in the cover sheet).

<sup>16</sup> For the purposes of this draft guidance, “registry” means an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more stated scientific, clinical, or policy purposes. Definition adapted from the Agency for Healthcare Research and Quality’s (AHRQ’s) “Registries for Evaluating Patient Outcomes: A User’s Guide,” available at <https://effectivehealthcare.ahrq.gov/products/registries-guide-4th-edition/users-guide>

<sup>17</sup> The use of the term “patient-generated data” is consistent with the use of this term in the “Framework for FDA’s Real-World Evidence Program” document, available at <https://www.fda.gov/media/120060/download>. Patient-generated data includes patient-generated health data. For the purposes of this draft guidance, “patient-generated health data” means health-related data created, recorded, or gathered by or from patients, family members, or other caregivers to help address a health concern. Definition adapted from <https://www.healthit.gov/topic/scientific-initiatives/pcor/patient-generated-health-data-pghd>

<sup>18</sup> For the purposes of this draft guidance, “digital health technology” means a system that uses computing platforms, connectivity, software, and/or sensors for health care and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, in a medical product, or as an adjunct to other medical products (devices, drugs, and biologics). They may also be used to develop or study medical products.

<sup>19</sup> In 2019, an outbreak of respiratory disease caused by a novel coronavirus began. The virus has been named “SARS-CoV-2,” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19). On January 31, 2020, the Secretary of Health and Human Services (HHS) issued a declaration of a Public Health Emergency

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- 219       • Clinically annotated biobanks; and  
220       • Medical device data repositories (e.g., imaging, electrocardiography databases).  
221

222 Some purposes for which use of RWD may potentially be applicable in a regulatory submission  
223 include the following:  
224

- 225       • To generate hypotheses to be tested in a clinical study;  
226       • As a historical control, an informative prior in a Bayesian analysis of a  
227       clinical trial,<sup>20</sup> or as one source of data in a hierarchical model or a hybrid  
228       data synthesis;  
229       • As a concurrent control group or as a mechanism for collecting data to support  
230       marketing authorization when a registry, EHR, claims data, or some other systematic  
231       data collection mechanism exists;  
232       • As a mechanism for re-training artificial intelligence/machine learning-enabled  
233       medical devices;  
234       • To generate evidence to identify, demonstrate, or support the clinical validity of a  
235       biomarker or clinical outcome assessment;  
236       • To generate (primary) clinical evidence to support marketing authorization (e.g.,  
237       HDE, PMA, 510(k) or De Novo request);  
238       • To generate evidence directly by the subject device to provide new information  
239       on safety or effectiveness;  
240       • To generate evidence to support a determination on whether the subject device  
241       meets the statutory criteria for a CLIA waiver<sup>21</sup> (e.g., CW and Duals<sup>22</sup>);  
242       • To generate evidence to support the interpretability of the primary clinical  
243       evidence (e.g., to demonstrate that the study population for an investigation  
244       conducted outside the United States (OUS) is representative of the US  
245       population, or to provide context for an adverse event observed in the clinical  
246       study);  
247       • To generate evidence to support a petition for reclassification of a medical device  
248       under section 513(e) or (f)(3) of the FD&C Act;

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(PHE) related to COVID-19 in accordance with section 319 of the Public Health Service Act (PHS Act) (hereinafter referred to as “section 319 PHE declaration”) and mobilized the Operating Divisions of HHS. In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19. The section 319 PHE declaration related to COVID-19 expired on May 11, 2023.

<sup>20</sup> For more information on Bayesian trials, see FDA’s guidance, “Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-use-bayesian-statistics-medical-device-clinical-trials-pdf-version>

<sup>21</sup> For more information on CLIA waiver by applications, see FDA’s guidance, “Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-clinical-laboratory-improvement-amendments-1988-clia-waiver-applications>

<sup>22</sup> For more information on the Dual 510(k) and CLIA Waiver by Application pathway, see FDA’s guidance, “Recommendations for Dual 510(k) and CLIA Waiver by Application Studies,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-dual-510k-and-clia-waiver-application-studies>. Dual De Novo classification requests and CLIA Waiver by Application for certain devices (see section 3301 of FDORA) should also consult this guidance.

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- To generate evidence for expanding the labeling of a device to include additional indications for use or to update the labeling to include new information on safety and effectiveness;<sup>23</sup>
  - To generate evidence for postmarket surveillance. Through ongoing surveillance, signals are at times identified that suggest there may be a safety issue with a medical device. RWE may be generated using RWD to refine these signals for purposes of informing appropriate corrective actions and communication;
  - To conduct post-approval studies that are imposed as a condition of device approval or to potentially preclude the need for 522 submissions; and
  - To provide postmarket data in lieu of some premarket data, consistent with FDA’s policy on balancing premarket and postmarket data collection.<sup>24</sup>

261

262

## **B. Application of Investigational Device Exemption (IDE) Requirements in 21 CFR 812 to the Collection of RWD**

263 An approved IDE permits a device to be shipped lawfully for the purpose of conducting  
264 investigations of the device without complying with certain other requirements of the FD&C Act  
265 that would apply to devices in commercial distribution. The purpose of this investigational  
266 exemption, per 21 CFR 812.1, “is to encourage, to the extent consistent with the protection of  
267 public health and safety and with ethical standards, the discovery and development of useful  
268 devices intended for human use, and to that end to maintain optimum freedom for scientific  
269 investigators in their pursuit of this purpose.” As explained in 21 CFR Part 812, the IDE  
270 regulations apply to all clinical investigations of devices to determine safety and effectiveness,  
271 with certain limited exceptions.<sup>25</sup> In many cases, an approved IDE is required before initiating a  
272 clinical investigation. An investigation is defined as “a clinical investigation or research  
273 involving one or more subjects to determine the safety or effectiveness of a device.”<sup>26</sup>

274

275 Whether the collection of RWD for a legally marketed device requires an IDE depends on the  
276 particular facts of the situation. Specifically, if the device is being used in the normal course of  
277 medical practice, an IDE would likely not be required. FDA recognizes that in clinical practice  
278 this could include use of a legally marketed device for uncleared or unapproved uses, where the  
279 device is being administered or prescribed under the authority of a health care practitioner within  
280 a legitimate practitioner-patient relationship. If data collection does not impact how the device is  
281 administered, and the administration is within the normal course of medical care, an IDE would  
282 likely not be required. For example, analyses of extant RWD (i.e., RWD already collected)  
283 involving the use in medical care of a device that was not within the cleared or approved  
284 indications for use would generally not be subject to IDE regulations. However, similar to

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<sup>23</sup> See FDA’s guidance, “General/Specific Intended Use,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/generalspecific-intended-use-guidance-industry>

<sup>24</sup> See FDA’s guidance, “Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval>

<sup>25</sup> See 21 CFR 812.2(a).

<sup>26</sup> See 21 CFR 812.3(h).

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285 traditional clinical studies, if data are being gathered to determine the safety and effectiveness of  
286 the device, and the process for gathering the data would influence treatment decisions, such  
287 administration would likely not be within the normal course of medical practice and an IDE may  
288 be required. For example, a study using a registry infrastructure designed to determine the safety  
289 and effectiveness of an approved device for a new intended use would likely be subject to IDE  
290 requirements if physicians are instructed to treat specific patients or otherwise administer the  
291 device in a prescribed way for purposes of data generation, or when certain follow-up activities  
292 are performed for the purpose of research.

293  
294 Should a sponsor or Institutional Review Board (IRB) be unclear regarding the applicability of  
295 the IDE regulations to a particular RWD collection activity or use, the sponsor or IRB should  
296 contact FDA. If an IDE is determined to be required, FDA intends to work with the IDE sponsor  
297 to develop the least burdensome approach to facilitate the efficient generation of RWE. Note that  
298 regardless of the applicability of 21 CFR Part 812, FDA regulations at 21 CFR Part 56 (IRB  
299 review), Part 50 (Protection of Human Subjects) and Part 54 (Financial Disclosure) may apply to  
300 RWE generation activities, as may other federal, state, and local laws regarding human subject  
301 protections.  
302

303 **C. Application of RWD from devices authorized for**  
304 **emergency use under section 564 of the FD&C Act**

305 Section 564 of the FD&C Act provides that FDA may, after the HHS Secretary has made a  
306 declaration of emergency or threat justifying authorization of emergency use (an “EUA  
307 declaration”), authorize the emergency use of an unapproved product<sup>27</sup> or an unapproved use of  
308 an approved product for certain emergency circumstances.  
309

310 The routine clinical use of a device authorized under an EUA, when used within the scope of its  
311 authorization, is not considered to be a clinical investigation (see section 564(k) of the FD&C  
312 Act and Section IV.B. for more information on the application of IDE requirements in 21 CFR  
313 Part 812 to the collection of RWD). Clinical data routinely collected from the use of a device  
314 authorized under an EUA may be considered RWD and may be used to support regulatory  
315 decision-making, if determined to be fit-for-purpose. Generally, the recommendations in this  
316 draft guidance may apply to RWD from devices authorized under an EUA. Additionally,  
317 Appendix B includes an example of RWD from a device authorized under an EUA that was used  
318 in a subsequent premarket submission.  
319

320 Device use pursuant to EUAs may lead to additional sources and novel uses of RWD to support  
321 FDA decision-making. We encourage sponsors to consider the recommendations in this guidance  
322 for devices authorized under an EUA (e.g., devices authorized under an EUA during the  
323 COVID-19 pandemic).  
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<sup>27</sup> Under sections 564(a)(2)(A) and 564(a)(4)(D) of the FD&C Act, an unapproved product is one that “is not approved, licensed, or cleared for commercial distribution under section 505, 510(k), 512, or 515 of [the FD&C] Act or section 351 of the [PHS] Act or conditionally approved under section 571 of [the FD&C] Act.”

## 325 **V. Assessing Data Relevance and Reliability**

326 To determine the potential suitability of RWD to generate RWE for regulatory decision-making,  
327 FDA assesses the relevance and reliability of the RWD source as well as the data elements, study  
328 design, and analytic components of the study. This section describes the elements that might be  
329 evaluated to determine if the data are fit-for-purpose. FDA recognizes that data, including RWD  
330 used to generate RWE, may have limitations. Sponsors should understand the strengths and  
331 limitations of generating evidence from RWD to address a specific study question and provide  
332 these limitations to FDA in their submission. If the RWD source appears relevant and reliable,  
333 then additional assessment of the study-specific derived dataset(s) may help demonstrate the  
334 RWD are fit-for-purpose to address the study question. This assessment may be used to  
335 determine whether the RWD source(s) and the proposed design and analysis can generate  
336 evidence that is sufficiently robust to be used for the given study question and regulatory  
337 purpose, i.e., whether the RWD are fit-for-purpose.

338  
339 Whether data are sufficiently relevant and reliable for use will, in part, depend on the particular  
340 regulatory decision. FDA will evaluate the same factors to assess RWD across all data sources  
341 and regulatory decisions but will weigh each factor in accordance with the regulatory decision to  
342 be made. In cases where RWE is derived from multiple RWD sources, each RWD source will be  
343 evaluated individually and together in the aggregate to determine the relevance and reliability of  
344 the RWD.

345  
346 The data should be accurate, as complete as possible, and of adequate data quality to credibly  
347 address the question at hand. Conducting a clinical investigation in accordance with GCP  
348 provides assurance that the data and results from the clinical investigation are credible and  
349 accurate and that the rights, safety, and well-being of subjects are protected.<sup>28</sup> In traditional  
350 clinical studies, the best practices for incorporating GCP into the study design and execution are  
351 generally well established. However, because RWD are typically collected outside of a  
352 controlled research setting, additional precautions should be considered to ensure that the data  
353 are similarly “credible and accurate,” and that appropriate patient protections are in place. In  
354 order to determine whether data are “credible and accurate,” FDA assesses the relevance and  
355 reliability of the data.

356  
357 Additionally, sponsors should ensure that RWD were collected using good data management  
358 practices and are sufficiently robust. Sponsors should also consider data related to various  
359 demographic characteristics (e.g., age, sex, race, and ethnicity)<sup>29</sup> and other potentially relevant

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<sup>28</sup> See, for example, 21 CFR 812.28(a)(1), which defines good clinical practice in the context of device investigations conducted outside the United States.

<sup>29</sup> For example, see the following FDA guidances: [Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-sex-specific-data-medical-device-clinical-studies-guidance-industry-and-food-and-drug); “Evaluation of Sex-Specific Data in Medical Device Clinical Studies,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-sex-specific-data-medical-device-clinical-studies-guidance-industry-and-food-and-drug>; and “Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-and-reporting-age-race-and-ethnicity-specific-data-medical-device-clinical-studies>

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360 covariates, and whether the data are representative of the intended use population. The relevance  
361 and reliability factors listed below should be described to assess the RWD.

362  
363 Studies using RWD should also be carefully designed to mitigate potential bias, and a study  
364 protocol and analysis plan should be created prior to analyzing RWD, regardless of whether the  
365 RWD are extant or if they are to be collected in the future. An existing RWD source may have  
366 some inherent sources of bias that could limit the relevance or reliability for drawing causal  
367 inferences between medical device exposures<sup>30</sup> and outcomes.

368  
369 To help ensure the relevance and reliability of the source data, FDA recommends sponsors  
370 consider the factors contained in this section. If considered, these factors should be referenced  
371 during study conduct, FDA inspection, or provided as additional information during FDA review  
372 of the applicable regulatory submission, as applicable. Appendix A sets forth the elements that  
373 FDA recommends sponsors document and have available for inspection, as well as  
374 recommended elements sponsors to include in the appropriate regulatory submission for FDA  
375 review.

376

#### 377 **A. Relevance**

378 Relevance includes consideration of availability, timeliness, and generalizability of the RWD.  
379 When needed information is not available in one data source, sponsors may want to provide  
380 linkage of other data source(s). Important relevance factors that FDA will consider in  
381 determining whether RWD are suitable for generating RWE for regulatory use include the  
382 following:

383

##### 384 **(1) Data availability**

385 The RWD should contain sufficient detail to capture the information needed to evaluate the  
386 question being addressed in the target population. Relevant considerations should include  
387 whether the RWD contains information on the following:

388

- 389 • Use of the device (e.g., the device identifier (DI)<sup>31</sup> portion of the unique device  
390 identifier (UDI),<sup>32</sup> other structured data, clinical notes) or other exposure in the study  
391 population;
- 392 • Outcome(s) of interest in the study population;

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<sup>30</sup> The exposure is the variable or data element whose causal effect is estimated in a study. For many studies supporting a regulatory submission, the exposure is the medical device. For some studies, especially those providing supportive clinical evidence, another exposure may be assessed to provide context for the use, safety, or effectiveness of the medical device within clinical practice.

<sup>31</sup> The device identifier is a mandatory, fixed portion of a UDI that identifies the specific version or model of a device and the labeler of that device. 21 CFR 830.3. For more information regarding UDI, see FDA's webpage <https://www.fda.gov/medical-devices/unique-device-identification-system-udi-system/udi-rule-guidances-training-and-other-resources>

<sup>32</sup> For class I devices, the universal product code (UPC) may serve as the UDI (21 CFR 801.40(d)). In these instances, the UPC should be included.

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- Covariates that may impact the exposure or outcomes of interest (e.g., RWD source contains signs, symptoms, treatments, procedures, diagnoses, patient and family history, pre-existing conditions, labs, demographics, and results which may be used to construct covariates that are relevant to the study question); and

397 For example, the minimum set of data fields in a registry may be

398 insufficient for a specific study question and additional data fields may

399 be needed for the registry to be fit-for-purpose. The registry should

400 retain information documenting the start or stop of collection during

401 the study time frame for data fields related to the specific study

402 question.

- 403
- 404
- Longitudinality, including longevity (the length of time that data for an individual is captured within the RWD source) and continuity of care.

405 Information across the continuum of care<sup>33</sup> (i.e., data observability)

406 may aid the assessment of the likelihood that all exposures and

407 outcomes of interest will be captured for regulatory decision-making.

408 For example, tertiary care hospitalization data may not have adequate

409 data availability to study outcomes that are likely to be diagnosed in an

410 emergency for all patients, because patients are likely to go to a nearby

411 hospital in emergencies but may travel to another location for a

412 specialty device procedure.

413

414 If the RWD source is insufficient on its own, the sponsor should determine whether

415 supplemental data sources are available and sufficient to provide any missing information

416 necessary to address the study question.

417

## 418 **(2) Linkages**

419 Sponsors should assess whether and how data from different sources can be obtained and

420 integrated given the potential for heterogeneity in target population characteristics, clinical

421 practices, and coding across data sources. A description of this assessment should be provided in

422 the regulatory submission for FDA review.

423

424 Any linkages performed within and across RWD sources should use a predefined linkage

425 methodology<sup>34</sup> that is scientifically valid, protects the privacy of individuals whose data will be

426 used, supports interoperability, and accounts for differences in coding and reporting across

427 sources. The following considerations should be assessed by the sponsor:

428

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- 431
- Adequacy of line-level linkages (i.e., that the same individuals are being matched), including pre-defined rules to check for logical consistency and value ranges to confirm that data were retrieved accurately from a linked data source; and

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<sup>33</sup> For the purposes of this guidance, “continuum of care” refers to the extent of the individual’s pertinent health data which is captured across settings/environments of care is represented in the RWD source.

<sup>34</sup> See An Overview of Record Linkage Methods - Linking Data for Health Services Research - NCBI Bookshelf, available at <https://www.ncbi.nlm.nih.gov/books/NBK253312/>

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- Application of strategies to correct for redundant data, to resolve any inconsistencies,  
433 and assess the potential for missing data.

434 Because patients typically visit multiple health care sites, especially in  
435 geographically contiguous areas, the inclusion of de-identified data  
436 from many sites creates the possibility that there will be multiple  
437 records from different health care sites for a single individual. This can  
438 result in overcounts of a particular data measure. Alternatively, if some  
439 site records are not available, this can result in a collection of histories  
440 that reflect only a fraction of the patient’s total health care history.  
441

### **(3) Timeliness**

442

443 As with traditional clinical studies, the time between data collection and release for research  
444 should be reasonable and the RWD considered for the study should reflect the current clinical  
445 environment (e.g., RWD from before a major change in clinical practice may not be timely).  
446 Sponsors should consider changes in clinical practice and guidelines over time (e.g., criteria for  
447 disease diagnosis, cancer staging), characteristics of a condition (e.g., prevalent strain of a  
448 pathogen) and health status of the population. If data are being collected within the RWD source  
449 during the study time frame, then the sponsors should update the availability of the RWD in a  
450 timely manner and should define the reporting schedule in the regulatory submission for FDA  
451 review.  
452

### **(4) Generalizability of data**

453

454 Once a study question is defined, the specific study sample meeting inclusion and exclusion  
455 criteria should be (1) representative of the population in the RWD source eligible for use of  
456 the device within the specified indication and (2) generalizable to the target population with  
457 the condition of interest. If upon quantitative assessment, the study sample is shown to not  
458 be representative of a subset of the target population, then analyses should be conducted to  
459 evaluate generalizability of the study findings.  
460

## **B. Reliability**

461

462 Reliability includes consideration of accrual, quality, and integrity of RWD. Important reliability  
463 factors that FDA considers in determining whether the RWD are suitable for generating RWE for  
464 regulatory use include the following:  
465

### **(1) Data Accrual**

466

467 To ensure the reliability of the RWD source, data should be collected and processed in a  
468 consistent and methodical manner. The manner of collection may differ for newly developed  
469 RWD sources which are actively collecting data (e.g., data dictionary to provide a common  
470 definitional framework in a registry), using nationally or internationally recognized coding  
471 systems (e.g., International Classification of Diseases, Tenth Revision, Clinical Modification  
472 (ICD-10-CM), Logical Observation Identifiers, Names, and Codes (LOINC), UDI, Current

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473 Procedural Terminology (CPT) in EHR or Claims) or custom-designed structured data capture  
474 (e.g., data capture within a device), or using unstructured data capture (e.g., narrative portion of  
475 clinical notes). Any of these approaches may be able to demonstrate sufficient reliability to  
476 support regulatory decision-making. Factors FDA will consider in making this determination  
477 include:

- 478
- 479 • Adequacy of information and descriptors about data sources provided in the  
480 regulatory submission for FDA review, which should include information on:
  - 481 • Data types;
  - 482 • Health care settings/environment(s);
  - 483 • Purpose of data collection;
  - 484 • How data were obtained at point of data capture;
  - 485 • How data are accessed by study team and sponsor;
  - 486 • Any data transformations, including any modifications made for privacy  
487 protection;
  - 488 • Full data dictionary or common data capture form, if applicable;
  - 489 • Device information, including types of identifiers (e.g., DI) and indication for  
490 use;
  - 491 • Completeness of fields that would typically be completed for all participants  
492 and needed for most study questions (e.g., age, sex, DI);
  - 493 • Time frame (including common temporal framework for collection of data)  
494 and latency of the data (including the timeliness of data entry, transmission,  
495 and availability);
  - 496 • Version control; and
  - 497 • Key technical and privacy-related information. Sponsors should document  
498 routine migration of data between various sources over time (e.g., indicate the  
499 date and time of data transfers, linkages).
- 500 • Adequacy of information about data accrual methods and procedures provided in the  
501 regulatory submission for FDA review, which should include information on:
  - 502 • Site collection procedures;
  - 503 • Use of common data capture forms;
  - 504 • Common definitional frameworks;
  - 505 • Data cleaning and cross-referencing procedures;
  - 506 • The sources and technical methods used for data element capture (e.g., chart  
507 abstraction, point of care entry, EHR integration, UDI capture, data records  
508 from the device, and linkage to administrative claims data); and
  - 509 • Methods for data retrieval and processes to minimize missing data extraction,  
510 implausible values, and data quality checks in data captured at the point of  
511 care (e.g., during clinical practice for manual or automated health care data  
512 collection processes) to ensure accuracy and completeness of core data fields.
- 513

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#### 514 (2) **Data Quality and Integrity**<sup>35</sup>

515 When considering RWD sources for regulatory purposes, sponsors should consider the methods  
516 and systems used to help ensure sufficient data quality, including any data quality assurance  
517 plans and procedures developed for the RWD source itself. Since evaluation of RWD sources  
518 may not always permit specific line-item source verification, important factors for sponsors to  
519 consider include:

- 520
- 521 • Quality control processes;
  - 522 • Regardless of the original purpose for collecting the RWD, procedures for
  - 523 data collection and quality assurance should be put into place during the data
  - 524 source design and development stages to optimize the reliability, quality, and
  - 525 usefulness of the data, as appropriate. These procedures should be described
  - 526 in the regulatory submission for FDA review.
  - 527 • Where appropriate, processes should include site and data monitoring, data
  - 528 quality audit programs, and evaluation of ongoing training programs for data
  - 529 collection.
  - 530 • Records regarding the assessment of adherence to the RWD source’s
  - 531 established data quality assurance and quality control policies and procedures
  - 532 should be retained.
- 533 • Assessment of completeness, accuracy, and consistency across sites and over time;
  - 534 • Data should be captured in a manner designed to minimize missingness.
  - 535 Missingness and out of range values should be assessed for each data element.
  - 536 The amount of missingness per participant (across data elements) should also
  - 537 be assessed. The impact of missingness should be considered and thresholds
  - 538 for unacceptable levels of missingness should be pre-determined.
  - 539 Additionally, quantitative assessment of the potential bias associated with
  - 540 high missingness should be performed and included in the interpretation of the
  - 541 study.
  - 542 • Data should be reflective of the actual patient experience (e.g., interactions
  - 543 with health care, disease trajectory, outcomes) with the condition of interest.
  - 544 • Consistency of data capture should be used across sites and over time.<sup>36</sup> If any
  - 545 changes are needed (e.g., where diagnostic criteria, definitions, or clinical
  - 546 practice change over several years), then sponsors should document those
  - 547 changes and assess their impact on the study question and provide summary
  - 548 information in the regulatory submission for FDA review.
  - 549 • Auditing rules, methods, and the mitigation strategies used to reduce errors
  - 550 should be documented.<sup>37</sup>

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<sup>35</sup> For more information on registry design and execution to better ensure data quality, sponsors can consult published literature such as: “AHRQ Registries for Evaluating Patient Outcomes: A User’s Guide,” 4th Edition, Section 1 Chapter 3, Registry Design and Section 3 Chapter 11, Obtaining Data and Quality Assurance, available at <https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-evaluating-patient-outcomes-4th-edition.pdf>

<sup>36</sup> More information on PCORI Conduct of Registry Studies is available at <http://www.pcori.org/sites/default/files/Standards-in-the-Conduct-of-Registry-Studies-for-Patient-Centered-Outcomes-Research1.pdf>

<sup>37</sup> For more information on documentation for FDA review, see Section VII. and Appendix A.

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- Study sample size should be adequate to address the study question.
    - If non-extant data are used (e.g., data for a newly marketed device will be captured in the future using the infrastructure of an existing data source), the sample size should be determined based upon adequate statistical power to detect a clinically meaningful difference.
    - If extant RWD are used, adequate statistical power to detect a clinically meaningful difference should be determined based on the available sample size and should account for any sampling of participants from the data source.
      - If there is inadequate statistical power based on the available sample size, sponsors should consider the use of multiple existing RWD sources to increase sample size.
      - If the sample size could be expected to increase in the near future (e.g., device is new to market), sponsors should consider conducting “interim” analysis with extant data, monitoring uptake, and conducting final analysis when sufficient sample size is available.
    - Sponsors should account for planned statistical analysis within the study size calculations (e.g., 1:1 matching of propensity scores in a study population where 10% of participants receive device would remove approximately 89% of participants with comparator from the analysis).
  - Establishment and adherence to data collection, recording, and source verification procedures;
    - As with all clinical evidence generation, data provenance and traceability are important. Sponsors should plan and document all aspects of data extraction, aggregation, curation, storage, and availability for research, as described below.
    - Sponsors should ensure any automated electronic transmission of data fields to a repository (e.g., registry or data warehouse) occurs in a consistent and reproducible fashion.
    - Adherence to source verification procedures and data collection and recording procedures should be documented for completeness and consistency.
    - Data checks and procedures should be prespecified to help address identified errors (e.g., in coding or interpretation of the source documentation or transformation).
    - Sponsors should describe the mitigations used to address audit findings, including data corrections.
    - Sponsors should identify the source document(s) and first instance<sup>38</sup> of data available to sponsor. Sponsors should generate data quality documentation

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<sup>38</sup> For the purposes of this draft guidance, the “first instance” is considered to be the data as initially available to the sponsor. For example, if the raw data from an EHR is available, then the first instance is at the point of capture for the data element. However, if the sponsor only has access to curated data or a specific dataset, then the “first instance” is the initially ingested data by the sponsor, even though it is not the original data collected.

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- 591 from the first instance through RWD dataset(s) used to address the study  
592 question.
- 593 • If using a common data model, sponsors should ensure documentation of the  
594 transformation of data from the original source to the common data model is  
595 retained.
  - 596 • Data audit trail, including assessment of discrepancies, should be included.  
597 For extant data sources, the sponsor may have access to the  
598 initial capture of data (e.g., direct access to EHR data as  
599 obtained via data entry) or may only have access to a partially  
600 curated data source (e.g., administrative claims data,  
601 aggregated EHR). We recommend sponsors maintain  
602 information on the data audit trail from the first instance of data  
603 available to the sponsor through all aspects of data analysis.  
604 Further, sponsors should obtain as much information as  
605 possible about the audit trail from the data holder if the first  
606 instance is not at the point of data entry.
  - 607 • When the RWD source is not owned by the sponsor, the sponsor should  
608 attempt to obtain participant-level data for each participant. If not available,  
609 the sponsor should define the entity(ies) which do have access/permission for  
610 data entry, quality assurance, storage, aggregation or other linkage, and  
611 assessment of traceability from data entry to dataset, as applicable. Sponsors  
612 should consider the level of access which could be shared with FDA and the  
613 potential for third parties to provide participant-level data directly to FDA.  
614 The availability of data should be described in the regulatory submission for  
615 FDA review.
  - 616 • As with all clinical evidence generation, FDA recommends that the sponsor  
617 have access to the RWD source from the first instance and to the RWD dataset  
618 used for the analyses throughout the regulatory decision-making process. FDA  
619 recognizes that some data sources will not allow sponsors to access the  
620 participant-level data. Although we do not discourage use of these data  
621 sources, FDA notes that uncertainty may arise if the sponsor does not have  
622 access to all of the necessary data.
  - 623 • Adequate patient protections (e.g., methods to protect the privacy of individuals'  
624 health data and adherence to applicable privacy and ethics standards) established in  
625 advance of executing the study protocol; and
  - 626 • Prior demonstration of RWE generation from the data source.
    - 627 • Sponsors should provide documentation (including fit-for-purpose  
628 assessment) of any previous use of the same RWD source for a similar target  
629 population and peer-reviewed literature of RWE generation from the data  
630 source.
- 631

## 632 **VI. Considerations for Methodologies for Collection and** 633 **Analysis of RWD to Generate RWE**

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634 A study using relevant and reliable RWD in a well-designed and rigorously analyzed manner  
635 may be less burdensome than a traditional clinical study. Just as traditional clinical studies  
636 should be carefully designed, studies using RWD also should undergo careful assessment before  
637 embarking on the study or during the analysis to assure that the data are fit-for-purpose. FDA  
638 recognizes that some regulatory decisions may not be adequately supported using RWE, for  
639 various reasons, and we therefore recommend that sponsors consider the methodologies  
640 described below to address factors that can impact interpretability of a study using RWD.

641  
642 Scientifically sound clinical study planning in advance of statistically valid analyses is important  
643 regardless of whether a study uses a traditional clinical study approach, uses only RWD, or  
644 incorporates a hybrid design. FDA recommends that any study be informed by the needs of the  
645 study question and regulatory decision driving the evidence generation. Further, just like for  
646 traditional clinical studies and in addition to the study design and analysis considerations  
647 described in Sections VI.A. and VI.B., FDA recommends that a sponsor document their  
648 decisions and the associated rationale for the following:

- 649
- 650 • Whether to include randomization, concurrent, or historical controls;
  - 651 • The choice of performance goals and objective performance criteria;
  - 652 • Type I and type II error control;
  - 653 • Data gathering or dependence on extant data;
  - 654 • Bias mitigation strategies;
  - 655 • Precision of outcome measures and other data elements, as applicable; and
  - 656 • All other known factors pertinent to interpretation of the study results.
- 657

658 Although many of the considerations in this section for data collection and analysis are not novel  
659 in the context of clinical evidence generation, there may be unique aspects of these  
660 considerations for studies using RWD. Additionally, the information presented in this section is  
661 intended to augment, not replace, information in other FDA guidances on the design of clinical  
662 studies for regulatory decision-making. The information in this section is intended to clarify  
663 implementation of these concepts and practices when using RWD. In particular, the information  
664 below is intended to complement information in the FDA guidance, “[Design Considerations for  
665 Pivotal Clinical Investigations for Medical Devices](#).”<sup>39</sup>  
666

#### 667 **A. Methods for study designs using RWD**

668 Generally, FDA does not endorse a specific type of study design for clinical studies, regardless  
669 of whether it is a traditional clinical study or uses RWD. As with all clinical evidence generation,  
670 choosing the appropriate design for studies using RWD depends on the study question, device,  
671 outcome, key covariates, and the specific study objectives or hypotheses. Additionally, sponsors  
672 should consider the regulatory purpose of the generated clinical evidence. FDA recognizes that  
673 multiple types of study designs may also be useful to generate RWE. These study designs may  
674 include:

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<sup>39</sup> Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices>

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- Single-arm studies with comparisons to external controls, in whole or part;
  - Objective performance criteria or performance goals;
  - Non-interventional studies (observational studies) (e.g., comparative cohort studies, case-control studies, self-controlled studies, and descriptive studies); and
  - Randomized controlled trials using RWD to supplement one or more study arms.

682 Furthermore, FDA recognizes the utility of RWD in assessing device utilization, participant  
683 characteristics, natural history of disease or disease trajectory, treatment environment and  
684 treatment patterns, as well as background rates of outcomes.<sup>40</sup>  
685

## 686 **B. Defining study design elements**

687 For studies using RWD, as with all clinical studies, after determining the overarching study  
688 design, the study time frame and collection of data elements should be defined, followed by a  
689 system to capture specific data elements (e.g., in a case report form). Additional data capture  
690 requirements may necessitate justification or adjudication, especially for study endpoints. FDA  
691 recommends clearly defining the individual data elements derived from the RWD source to  
692 develop study-specific RWD. Similarly, FDA recommends that sponsors show that the data  
693 elements, as defined and applied within the study design, are relevant, reliable, and fit for the  
694 regulatory purpose. For analysis of RWD and interpretation of RWE, sponsors should have a  
695 study design that describes the study time frame, the pre-defined set of data elements, and a  
696 systematic consideration that the proposed data elements are all necessary for inclusion and  
697 represent all the key data elements.  
698

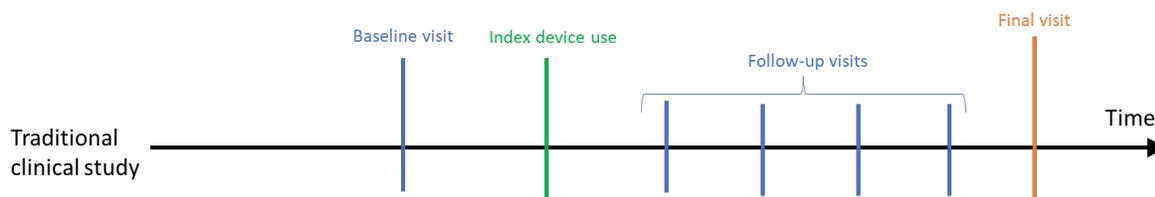
### 699 **(1) Study time, relative to index date**

700 In traditional clinical studies, a participant is often enrolled into the study, has a baseline visit,  
701 and then first uses the device or has a procedure on the “index date” (see Figure 1). After that,  
702 the participant is usually followed for a period of time until a final visit. Data elements are  
703 collected at each visit, although different information may be gathered at each visit, and  
704 additional data elements may be collected outside of clinical care (e.g., via a participant diary or  
705 wearable). The participant continues to be followed through a last study visit. If a visit or other  
706 data collection is missed, then the participant may be contacted, or additional questions may be  
707 asked at the next visit to gather key information.  
708

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<sup>40</sup> Such uses of RWD, while beyond the scope of this draft guidance, may be valuable for describing the clinical context in which the device will be used, to support a diversity action plan. *See* section 520(g)(9) of the FD&C Act for more information on diversity action plans for medical devices.

709 **Figure 1. Traditional clinical studies - study time frame relative to index date**



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711

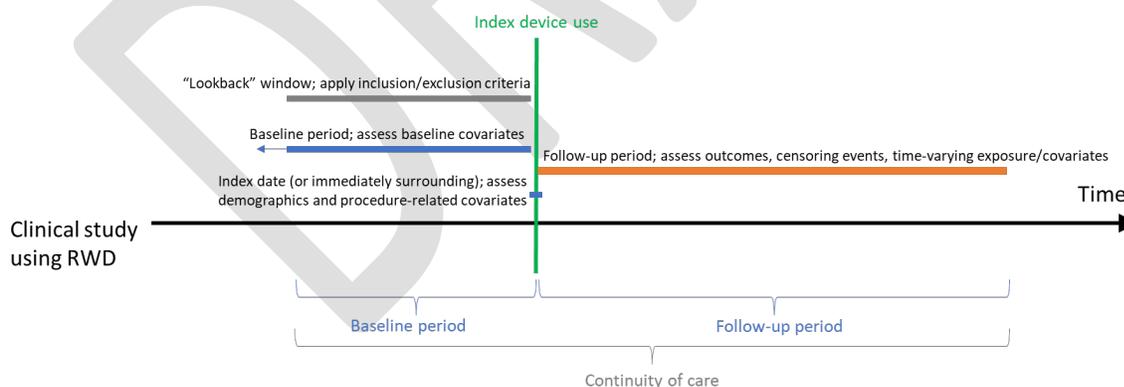
712 In clinical studies using RWD where data are collected after the study is designed, it is possible  
713 that a similar visit structure and data collection will be available (e.g., within a registry).  
714 However, follow-up visits may not occur on a set schedule or more patient-generated data may  
715 be collected. For extant data such as EHR or administrative claims, baseline and follow-up data  
716 are not collected on a set schedule; rather data collection coincides with clinical care over a  
717 period of time (see Figure 2). Participants may also enter or exit the source database as their life  
718 situation changes (e.g., move out of a geographic area or a change in health insurance). Thus,  
719 continuity of care is an embedded part of the study.

720

721 A visual depiction, such as that exemplified in Figure 2, may be helpful in identifying the timing  
722 of collection for each data element relative to the index date, which will help to identify potential  
723 bias. Data elements that may impact the initial device use should be collected before or at the  
724 time of initiation. Outcomes of device use occur after use of the device is initiated. Additionally,  
725 the index date for the use of the comparator to the device would occur at a similar point in the  
726 progression of disease. As with a traditional clinical study, discussion of these ideas with the  
727 study team or with FDA may be aided by the visual depiction of when each data element will be  
728 assessed.

729

730 **Figure 2. Clinical study using RWD - study time frame relative to index date**



731  
732

733 Follow-up in a study using RWD typically extends from the index date of device use until either  
734 the end of the pre-planned follow-up time or the last time identified within the RWD source.  
735 FDA considers the study end date to be the last date that participant follow-up could occur. This  
736 date is set on a day when data checks/audits can assure that the underlying data are of sufficient  
737 quality for use in research. Any data in the RWD source indicating that a participant had

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738 subsequent care is no longer included in the study (i.e., study participation is censored on this  
739 date). Thus, similar to the first site being ready for enrollment in traditional clinical studies, FDA  
740 expects that the study time frame will be defined to begin on the earliest date that the first data  
741 element could be collected and extend through the latest date that the last data element could be  
742 collected.

743  
744 In addition to the study design elements discussed above, any change in the standard of care,  
745 availability of the device or other treatments, or other relevant factors (e.g., change in hospital  
746 care due to a public health emergency) should be included on the graphical depiction. This  
747 additional information may aid in systematically capturing these time-dependent data elements  
748 and provide support for their inclusion as covariates in analyses or consideration of sensitivity  
749 analysis (e.g., assessing whether a change in ICD-CM coding from a prior edition or a major  
750 change in clinical practice affects study results).

751  
752 The calendar time allotted for the study should be long enough to adequately measure all data  
753 elements in a study – from the beginning of the baseline period through the end of the follow-up  
754 needed to assess the outcome(s) of interest – in a sample of participants large enough to provide  
755 adequate statistical power to detect the minimal clinically important difference in the primary  
756 outcome.

757

#### 758 **(2) Development of conceptual and operational definitions for** 759 **the study population, device, comparator, outcome, and** 760 **covariates**

761 As with any clinical study, all data elements should be defined before the start of a study using  
762 RWD and should address the specific study question when valid and appropriate analytical  
763 methods are applied (i.e., the data are amenable to sound clinical and statistical analysis). A  
764 “conceptual definition” that describes the construct or feature of each data element in general or  
765 quantitative terms should be generated using a shorthand name or notation. This conceptual  
766 definition should reflect the current medical and scientific thinking regarding the variable of  
767 interest, such as: (1) clinical criteria to define a condition for population selection or as an  
768 outcome of interest or a covariate; or (2) measurement of the device or procedure to define an  
769 exposure of interest. For example, a conceptual definition might be “acute myocardial infarction  
770 (AMI)” or “AMI evidenced by increased troponin.” For a traditional clinical study, the sponsor  
771 defines the collection and timing of each data element, whether at a visit or between visits, and  
772 usually has the ability to contact the participant to limit missing data or to solicit additional  
773 information if a visit was missed. In a study using RWD, the data elements may be collected in a  
774 similar fashion (e.g., registry) or need to be defined from clinical care visits (e.g., EHR or  
775 administrative claims data) or some other algorithm (e.g., combining unstructured EHR and  
776 patient-reported data).

777  
778 An “operational definition” describing all of the components needed to identify complete and  
779 accurate data elements from the data source should also be generated. While an operational  
780 definition would typically be generated in a case report form in a traditional clinical study,  
781 operational definitions in a study using RWD frequently include combining structured codes or

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782 unstructured notes (e.g., clinical notes) in an algorithm to identify presence of the data element.  
783 FDA considers the operational definition to include three components, as applicable:  
784

- 785 • Time frame over which assessment occurs;
- 786 • Specific codes/component(s) assessed (e.g., via code lists); and
- 787 • Algorithm for combining the components (leading to positive identification or lack of  
788 identification). If machine learning is used to define criteria, sponsors should provide  
789 a full description of data management practices including the specifications of the  
790 model/algorithm (e.g., training, tuning, and testing), data collection and the data  
791 attributable to the proposed intended use population (e.g., with respect to race,  
792 ethnicity, disease severity, sex, gender, age, socioeconomic characteristics), as well as  
793 verification and validation information to indicate that the machine learning  
794 approaches are fit-for-purpose for defining criteria.  
795

796 The availability of different data types in studies using RWD may make it possible to establish  
797 operational definitions that are different from those typically used in traditional clinical studies.  
798 These definitions may or may not be appropriate in the context of the study question being  
799 addressed depending on the study question and regulatory purpose. It is important to consider  
800 whether the operational definition will capture the intended concept for each data element and  
801 FDA notes that small differences in the choice of operational definition in a specific data source  
802 (e.g., requiring two diagnoses rather than one diagnosis of AMI in the example above) may have  
803 a large impact on study results (e.g., considerably decrease the identification of the disease or  
804 condition under study). FDA considers minimizing misclassification to be a critical part of the  
805 process of defining an operational definition. FDA recommends reviewing previous studies using  
806 the RWD source, including published literature, and gathering expert opinion when developing  
807 operational definitions. For some data elements, a rationale for the operational definition based  
808 on previous studies or expert opinion may be sufficient. Some data elements may warrant more  
809 scrutiny to ensure that the interpretation of study results is not substantially impacted by their  
810 misclassification or missingness.  
811

812 In some cases, it may be appropriate to conduct a validation study in which quantitative  
813 measurements of the operational definition are compared to a “ground truth” reference standard.  
814 This may result in updating the operational definition to ensure that these critical data elements  
815 are accurately identified. When conducting a validation study, a protocol should be developed  
816 before initiating the data collection and analysis specific to the validation. The protocol generally  
817 contains the plan to compare the operational definition in the RWD (e.g., administrative claims  
818 data) with the “ground truth” in the reference standard (e.g., validating that administrative billing  
819 diagnosis accurately represents a point-of-care diagnosis by comparing an operational definition  
820 in administrative claims against an EHR) and prespecification of the acceptance criterion for  
821 each validation measure (e.g., sensitivity, specificity, or positive and negative predictive values)  
822 which is of interest.  
823

824 As with traditional clinical studies, in choosing existing operational definitions or developing  
825 new ones, sponsors should maximize identification of those who have the condition and to  
826 minimize incorrectly identifying those without the condition as having it (i.e., minimize

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827 misclassification). Sponsors can check for misclassification, for example, by generating a table  
828 of the proportions of participants within the study who are at each level of each data element and  
829 performing a qualitative comparison to what is known from previous literature or expert opinion  
830 about that data element in the target population. Further exploration is recommended for data  
831 elements that are not aligned with expectation. This same exercise may help identify any under-  
832 recording or missingness of data elements within the study.

833  
834 In some RWD sources, the data elements that would be preferred for traditional clinical studies  
835 may not be available to the sponsor. However, a proxy for this missing information could be  
836 developed based on the information that is collected in the RWD source. Proxies can be  
837 developed for a wide range of uses, including identifying study participants (i.e., applying  
838 inclusion/exclusion criteria) as well as certain study endpoints. It may be possible to use the  
839 proxy, but sponsors should determine the suitability of a proxy by considering whether the proxy  
840 is clinically relevant and may call for additional data gathering or conducting validation of the  
841 proposed operational definition for the data element, if using the proxy adds too much  
842 uncertainty to the study interpretation. FDA encourages use of measures that participants or  
843 practicing clinicians deem meaningful as potential data elements for studies using RWD.  
844 Development of endpoints or potential consideration of proxy outcomes may be warranted to  
845 address some study questions. Additionally, development of proxies for key covariates may also  
846 be appropriate to address some study questions.

847

### 848 **(3) Appropriate integration of data elements within study** 849 **design and analysis**

850 As with all clinical evidence, data elements in a study using RWD should be determined before  
851 conduct of the analysis and integrated into the study design and analysis in a manner which  
852 allows for assessment of the study question. Once the device and outcome are determined per the  
853 study question, variables which affect both the device and outcome (i.e., confounders) should be  
854 addressed within the study design and analysis to minimize bias and uncertainty. Differing levels  
855 of influence may exist and both direct and indirect influences on the device or outcome may exist  
856 for a confounder. Thus, only a subset of the confounders initially identified should be included in  
857 the study. Conversely, variables that are impacted by the device and subsequently impact the  
858 outcome (sometimes called “mediators” or “intermediate variables”) should be carefully  
859 considered before inclusion in evaluations of how the device impacts the outcome. Depending on  
860 the type of analysis, inclusion of such variables may dilute the totality of the device impact. As  
861 with all clinical studies, subgroup analyses for sex, age, racial or ethnic groups are expected  
862 because there may be differential effects of the outcome for participants across these  
863 subgroups.<sup>41</sup> Other variables may also exhibit heterogeneity in risk of the outcome (i.e.,  
864 modifiers or “interaction” terms) and stratified analyses for these variables may also be  
865 appropriate.

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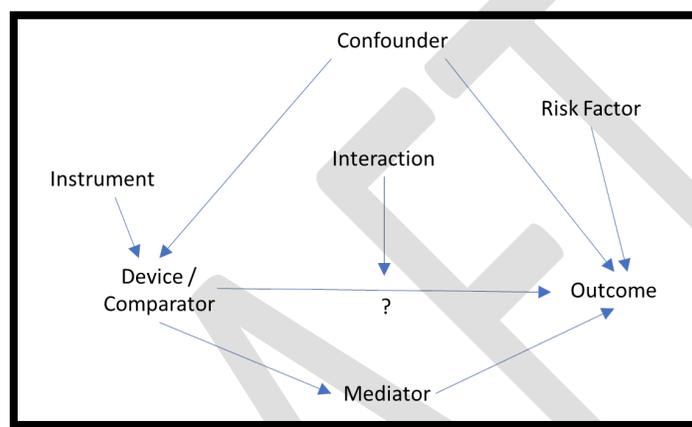
<sup>41</sup> See FDA’s guidances, including, [Evaluation of Sex-Specific Data in Medical Device Clinical Studies](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/collection-race-and-ethnicity-data-clinical-trials); “Collection of Race and Ethnicity Data in Clinical Trials,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/collection-race-and-ethnicity-data-clinical-trials>; and [Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-and-reporting-of-age-race-and-ethnicity-specific-data-in-medical-device-clinical-studies)

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867 One way to identify which data elements fall into each of these types of variables is to generate  
868 and analyze causality diagrams. Causality diagrams (e.g., directed acyclic graphs, see Figure 3)  
869 and their subsequent assessment may provide a rationale for the design and analysis choices.  
870 Additionally, causality diagrams may provide a resource to aid discussions for a study design  
871 amongst the study team or with FDA. Covariates affecting and affected by both the exposure and  
872 outcome are noted within the causality diagram, irrespective of availability within RWD, and are  
873 assessed for potential relationships between the variables.  
874

875 **Figure 3. Directed acyclic graph to identify potential data elements and assess which are**  
876 **key for the study question**



877  
878

## 879 **VII. Documentation for FDA Review**

880 This section describes the documentation recommended to support the use of the RWD for  
881 generating RWE for regulatory purposes and applies to device regulatory submissions submitted  
882 to CDRH and CBER, including but not limited to, pre-submissions, 510(k)s, PMAs, BLAs,  
883 HDEs, De Novos, IDEs, post-approval study PMA supplements, 522 submissions, CLIA Waiver  
884 by Applications, and Duals.  
885

### 886 **A. Regulatory Submission Cover Letters**

887 FDA recommends sponsors identify RWD and RWE as part of the regulatory submission cover  
888 letter to help facilitate review and internal tracking. Specifically, FDA recommends sponsors  
889 include the following elements in the cover letter for each submission that includes RWD:  
890

- 891 • Purpose of using RWE to support the submission (see list of examples in Section  
892 IV.A.);
- 893 • Description of where the RWE fits into the totality of clinical evidence submitted  
894 (e.g., to support interpretability of the primary evidence, to establish a performance  
895 goal, to supplement clinical evidence) (see list of examples in Section IV.A.);
- 896 • Study design (i.e., type of study) using RWD to generate RWE (see list of examples  
897 in Section VI.A.);

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- RWD source(s) used to generate RWE (see list of examples in Section IV.A.); and
  - Specific RWD source(s) and version, including the following information, if applicable:
    - Data source name;
    - Data source provider;
    - Version number; and
    - Date of extraction and date range of data extracted.

### **B. Fit-For-Purpose Assessment**

906

907 If sponsors include RWE in support of regulatory submissions, they should include their fit-for-

908 purpose assessment of the relevance and reliability of the RWD to generate RWE with the

909 following elements:

910

- 911
- 912
- 913
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- 918
- An assessment of the key relevance and reliability factors for the study using RWD (see Section V.), which may include, but is not limited to the following:
    - Data availability, linkages, timeliness (see Section V.A.);
    - Data accrual, quality and integrity (see Section V.B.);
    - Study purpose, specific data elements, generalizability of data, assessment of confounding, timing of data availability (see Sections V.A. and VI.B.); and
    - Completeness and accuracy of study sample reflecting the target population, study design and planning (see Section V.B.2.).

919 In addition to the fit-for-purpose assessment of the RWD, we recommend that the sponsor

920 provide the following contextual information regarding how the generated RWE fits into the

921 totality of evidence:

922

- 923
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- 929
- A description of how the RWE is being used in the totality of clinical evidence submitted to FDA;
  - A summary of how the totality of the relevance and reliability of the RWD is fit-for-purpose to address the study question; and
  - If unique considerations for the specific RWD source exist, sponsors should describe these considerations and how they impact the overall assessment of the data.

### **C. Protocol**

930

931 As with traditional clinical studies, sponsors should submit the protocol as part of the regulatory

932 submission to FDA. In studies designed to test a hypothesis, FDA recommends that sponsors

933 finalize the protocol and analysis plan prior to reviewing the outcome data of a study and before

934 performing the prespecified analyses. Sponsors should indicate in the regulatory submission

935 whether or not the protocol and analysis plan were finalized prior to the analyses. In addition,

936 individuals generating summary scores (e.g., propensity score modeling) should not have access

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937 to the outcomes within the dataset(s) used for the study. Any revisions to the protocol should be  
938 dated and time-stamped, and the rationale for each change should be provided.

939  
940 Similar to protocols submitted with traditional clinical studies, sponsors should consider  
941 providing the following information in the protocol for the study generating the RWE, when the  
942 RWD or RWE is included in the regulatory submission:

- 943
- 944 • Study synopsis;
  - 945 • Background and study purpose;
    - 946 • Explanation of how the source data is or is not representative of the general
    - 947 disease/population with the condition, including sufficient previous research
    - 948 to interpret study results within the context of the target population, disease
    - 949 trajectory, and current clinical care; and
    - 950 • Description of the device included in the study, including the DI portion of the
    - 951 UDI, if available. For devices excepted from the UDI requirements, sponsors
    - 952 should include the version(s) of the device.
  - 953 • Study aims and objectives;
  - 954 • Study design, including study period;
  - 955 • Study design diagrams are suggested to clarify (1) potential study entry dates within
  - 956 study period and (2) assessment of all other data elements in relation to cohort entry
  - 957 or index date (causality diagram recommended);
  - 958 • Data source, including a description of how the setting/environment(s) of data capture
  - 959 provided adequate continuity of care (see Section V.B.);
    - 960 • Identification of any common data model structure used for housing the RWD
    - 961 source or for transformed study-specific RWD, if applicable.
  - 962 • Data elements (conceptual and operational definitions for all), including:
    - 963 • Determination of initiation, continuance, and discontinuation of device
    - 964 exposure, if applicable (see Section V.B.);
    - 965 • Study population, including inclusion and exclusion criteria;
    - 966 • Device and comparator, if included in the study;
    - 967 • Outcome and endpoints; and
    - 968 • Covariates.
  - 969 • Statistical/data analysis plan;
  - 970 • Data management and quality control plans (see Section V.B.);
  - 971 • Sample size and statistical power;
  - 972 • Description of human subject protections, as appropriate, including informed consent,
  - 973 IRB determination, deidentification plan (e.g., to remove participant identifiers from
  - 974 patient-generated data or device-generated data), and data confidentiality plans;
  - 975 • Plans for adverse event reporting;<sup>42</sup>

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<sup>42</sup> See 21 CFR part 803.

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- Milestones and timeline;
  - Auditing and monitoring plans, as applicable;
  - If validation or adjudication of data element(s) were conducted (see Section VI.B.), sponsors should include the study plan and results for validation or adjudication; and
  - A copy of the data dictionary used, if one was used or developed.

#### **D. Report**

982

983 As with traditional clinical studies, sponsors should submit the report as part of the regulatory

984 submission to FDA. The report should include the occurrence and rationale for any protocol

985 deviations.

986

987 Additionally, in a regulatory submission with a report of a study using RWD, the study results,

988 discussion, and conclusion should be included, including how the RWE supports the purpose of

989 the submission. Specifically, sponsors should include the following information:

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- 994
- 995
- Date of data extraction (see Section V.B.);
  - All elements from the protocol, updated to reflect how the study was conducted; and
  - Justification that any changes or modifications to the protocol did not affect the validity of the resulting RWE.

#### **E. Additional Information**

996

997 As with traditional clinical studies, sponsors should also provide the following information in

998 regulatory submissions that include RWE:

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- 1000
- 1001
- 1002
- 1003
- 1004
- 1005
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- 1007
- 1008
- ClinicalTrials.gov National Clinical Trial (NCT) Number,<sup>43</sup> if applicable;
  - Informed consent and IRB documentation, as applicable;
    - Initial and continuing IRB review and approval; and
    - Initial and approved changes to informed consent.
  - List of investigational sites, if any, including mailing address, contact information, and investigator name; and
  - Case Report Form templates, as developed by the sponsor, if applicable (e.g., these templates may be helpful if EHR or claims data are not mapped to the dataset from the source).

1009

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<sup>43</sup> ClinicalTrials.gov assigns a unique NCT number to each clinical study registered on their webpage. See <https://clinicaltrials.gov/> for more information.

1010 **Appendix A. Recommended Elements for Documentation**  
 1011 **and FDA Review**

1012 The following is an example of the recommended elements to assist sponsors and FDA in  
 1013 determining relevance and reliability of the RWD. The tables below summarize the  
 1014 recommended elements identified throughout the guidance for sponsors to document and provide  
 1015 in FDA submissions, and the recommended locations for where to include this information. The  
 1016 tables are not intended to serve as either a mandatory or exclusive checklist. Rather, the tables  
 1017 provide a simplified summary of the key elements that sponsors should use to assess relevance  
 1018 and reliability.

1019  
 1020 **Table 1- Recommended RWD Relevance Elements for Submission of RWE**  
 1021

<b>Item (Linked to Section V.)</b>	<b>Information for Sponsors to Document (e.g., to make available for inspection)</b>	<b>Information for Sponsors to Provide to FDA in Submission</b>	<b>Recommended Location in FDA Submission</b>
Determine RWD source contains sufficient detail to capture data elements and address the study question	x (detailed)	x (rationale)	Protocol (rationale for study question and data element definitions)
Assess longitudinality of data source		x	Protocol
Assess continuity of care in data source		x	Protocol and report
Ensure reasonable time between data collection and release for research		x	Protocol and report
Consider changes in clinical practice/guidelines over time	x	x	Protocol
Assess timing of availability of any new (i.e., updated) data after initial data availability		x	Protocol and report
Assess whether and how data from different sources can be obtained and integrated, given the potential for heterogeneity in population characteristics, clinical practices, and coding across data sources		x	Protocol
If done, use of a predefined linkage methodology that is scientifically valid and accounts for differences in coding and reporting across sources	x (detailed)	x (high level)	Protocol

**Contains Nonbinding Recommendations**

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<b>Item (Linked to Section V.)</b>	<b>Information for Sponsors to Document (e.g., to make available for inspection)</b>	<b>Information for Sponsors to Provide to FDA in Submission</b>	<b>Recommended Location in FDA Submission</b>
Assess adequacy of line-level linkages		x	Report
Correct for redundant data, to resolve any inconsistencies, and assess the potential for missing data	x		
Demonstrate interoperability of the linked data systems	x		
Ensure study sample is representative and generalizable to RWD source and target population		x	Protocol and report

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1024

**Table 2- Recommended RWD Reliability Elements for Submission of RWE**

<b>Item (Linked to Section V.)</b>	<b>Information for Sponsors to Document (e.g., to make available for inspection)</b>	<b>Information for Sponsors to Provide to FDA in Submission</b>	<b>Recommended Location in FDA Submission</b>
Establish information and descriptors about data source(s)		x	Protocol
If applicable, describe defined processes, site training, support, qualified personnel for complete and accurate data collection	x		
Document routine migration of data from various sources over time	x		
Describe sources and technical methods used for data element capture	x		
Describe methods for data retrieval and processes to minimize missing data extraction, implausible values, and data quality checks	x		
If not data holder, describe level of access, attempt to gain patient-level data, and consider access for FDA		x	Protocol
Describe the quality of the data captured	x (detailed)	x (high level)	Report

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<b>Item (Linked to Section V.)</b>	<b>Information for Sponsors to Document (e.g., to make available for inspection)</b>	<b>Information for Sponsors to Provide to FDA in Submission</b>	<b>Recommended Location in FDA Submission</b>
Plan and document the process of extraction, aggregation, curation, storage, and availability of data for research	x		
Describe data flow from first instance to data source instance as housed by sponsor	x		
Define and follow procedures for data collection and quality assurance	x		
Provide assessment of completeness, accuracy, and consistency across sites and over time		x	Report
Assess consistency of data capture across sites and over time; if any changes are needed (e.g., diagnostic criteria or clinical definitions change in the course of clinical practice over several years), then document those changes and assess their impact on the study results	x (detailed)	x (high level)	Report
Assess missingness and out of range values for each data element		x	Protocol and report
Ensure data elements captured and included in the study are reflective of the actual patient experience (e.g., interactions with health care, disease trajectory, outcomes) with the condition of interest		x	Protocol and report
Define the auditing rules and methods used and the mitigation strategies used to reduce errors	x		
Ensure study size is adequate to address the study question with adequate statistical power and accounting for planned analyses		x	Protocol and report
Document adherence to source verification procedures and data collection and recording procedures for completeness and consistency	x		
Prespecify data checks and procedures to help address identified errors	x		

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

<b>Item (Linked to Section V.)</b>	<b>Information for Sponsors to Document (e.g., to make available for inspection)</b>	<b>Information for Sponsors to Provide to FDA in Submission</b>	<b>Recommended Location in FDA Submission</b>
Describe mitigations to address audit findings, including data corrections	x		
Securely store data and ensure appropriate permissions/agreements for access	x		
Provide documentation of any previous RWD source fit-for-purpose assessment for a similar target population and all peer reviewed literature of RWE generation from data source		x	Protocol
Ensure adequate patient protections (e.g., methods to protect the privacy of individuals' health data and adherence to applicable privacy and ethics standards) established in advance of executing the study protocol		x	Protocol and report

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## 1026 **Appendix B. Examples Where RWE is Used**

1027 Most of the following examples are generalized from actual uses of RWD in support of FDA  
1028 regulatory decision-making. These examples do not represent a comprehensive list of all  
1029 potential uses or sources of RWD but do describe some situations where RWE might be used to  
1030 support regulatory decision-making. For additional examples of RWE used in regulatory  
1031 decisions, see the following FDA document: [Examples of Real-World Evidence \(RWE\) Used in](#)  
1032 [Medical Device Regulatory Decisions](#).<sup>44</sup>  
1033

### 1034 **Example 1: New or Expanded Indications for Use**

1035 An implanted device, which was available outside the US (OUS), used RWE as the primary  
1036 clinical evidence to support the original PMA submitted to FDA. RWD from an OUS registry in  
1037 one country, which included nearly 300 patients with more than two years of follow-up, was  
1038 compared against a performance goal (PG) for device effectiveness. The PG was derived from a  
1039 prospectively defined, systematic meta-analysis of available published literature and registry data  
1040 for a control device legally marketed in the United States. The study prospectively evaluated the  
1041 functional outcome and patient satisfaction for multiple devices. The safety assessment was  
1042 based on a comparison of the serious device related adverse event rates for the subject device to  
1043 the rates extracted from the registry and the same literature studies used to derive the PG. These  
1044 analyses served as the primary basis supporting approval of the PMA. In this example, an IDE  
1045 was not needed for the study as the clinical data for the subject device was obtained from extant  
1046 data in an OUS registry.

1047  
1048 Should a manufacturer wish to expand indications, this type of RWD might be used to generate  
1049 sufficient evidentiary support, depending on the specific devices, indications, and analyses.  
1050

1051 Another example is an implanted device that was available on the US market for several years  
1052 for one indication for use. The sponsor submitted a PMA panel-track supplement to support  
1053 expanding indications for this device. Supplemental clinical evidence for safety of the indication  
1054 expansion was provided from the sponsor's patient database, with more than 36,000 patients,  
1055 linked with Medicare claims. The RWE characterized the 12-month safety profile of patients  
1056 with the specific condition (i.e., new indication) implanted with the device and assessed the  
1057 safety among patients receiving the implant and diagnosed with the specific condition compared  
1058 to patients implanted with the device that did not have the respective condition. The sponsor's  
1059 patient database and Medicare claims were linked using probabilistic methods (i.e., based on date  
1060 of birth, implant date, implant clinic). A systematic review of literature was also conducted to  
1061 identify diagnostic codes associated with safety outcomes. In this example, an IDE was not  
1062 needed for the study as the clinical data for the subject device was obtained from extant data.  
1063

### 1064 **Example 2: 522 Submissions**

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<sup>44</sup> Available at: <https://www.fda.gov/media/146258/download>

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1065 The manufacturer of a class II designated software-only device was subject to a postmarket  
1066 surveillance order for this device under section 522<sup>45</sup> of the FD&C Act, as it met the statutory  
1067 criteria that its failure would be reasonably likely to have serious adverse health consequences,  
1068 and it also was expected to have significant use in pediatric populations.

1069  
1070 Following discussions with the FDA, the postmarket surveillance study for this software-only  
1071 device was a single-arm, prospective study designed to assess the 12-month safety in a real-  
1072 world setting and to support the continued assessment of the software for its intended use. It  
1073 included both pediatric and adult populations. The outcomes were evaluated versus a comparator  
1074 group, which was determined using evidence from a systematic literature review of similar use in  
1075 the intended use population. Device-related adverse events were recorded electronically from  
1076 both inbound reports from customers and assessed through outreach to patients. The safety  
1077 endpoints included the risk for adverse events as extracted in the literature review. Besides the  
1078 safety and effectiveness endpoints, the study also included a secondary endpoint of patient-  
1079 reported satisfaction with and trust in the software-only device. At the end of the study, the  
1080 device had met its endpoints, and there were no unanticipated adverse device effects.

1081

#### **Example 3: Control group**

1082 A sponsor submitted a PMA panel track supplement to support an indication expansion  
1083 supported by a single-arm study compared to a control group of patients enrolled in a US registry  
1084 receiving alternative devices for the new disease condition. The alternative devices were  
1085 identified through the use of UDI. To account for potential differences between the device and  
1086 control groups, the sponsor performed a propensity-score adjusted analysis using 20 pre-  
1087 specified variables. The propensity score results were reviewed by FDA before the sponsor  
1088 performed the outcome analysis. Sensitivity analyses were conducted to assess the impact of  
1089 missing data. The registry did not routinely collect all relevant data for the control group,  
1090 therefore, additional information for patients in the registry was collected from extant EHRs. The  
1091 results of these analyses demonstrated that the success criteria were achieved.

1092

1093  
1094 Along with analyses of serious adverse events from the sponsor's global study, this RWE was  
1095 the primary basis for supporting approval of the PMA supplement.

1096

#### **Example 4: Supplementary Data**

1097 A sponsor submitted a De Novo request for a device. Although the sponsor conducted a  
1098 prospective, repeated measures, single arm study as the primary clinical evidence to support  
1099 safety and effectiveness for their De Novo request, RWD from a chart review at a single site was  
1100 used as supplemental evidence. The overall objective of the study using RWD was to confirm the  
1101 performance of the subject device as part of the standard of care and to further investigate trends  
1102 in treatment outcomes for patients with different severities of the disease. The RWE generated  
1103 from this data provided clinical practice results for a patient population that was not included in  
1104

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<sup>45</sup> FDA has issued a series of postmarket surveillance orders, related to investigating patient safety issues for a type of class II device, under the authority of section 522 of the FD&C Act. These 522 orders cover multiple devices from different manufacturers that are similar in intended use, design, and other characteristics, such that the surveillance questions are identical.

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1105 one of the clinical studies and demonstrated consistent outcomes with the prospective single arm  
1106 study.  
1107

#### **1108 Example 5: RWE Obtained from Use of EUA device**

1109 In response to the COVID-19 outbreak, FDA authorized the emergency use of certain devices  
1110 under section 564 of the FD&C Act.<sup>46</sup> A sponsor of a serology test authorized for emergency use  
1111 used RWD from a patient registry to support the expansion of the intended use (i.e.,  
1112 asymptomatic testing when authorized only for symptomatic testing) in a subsequent Dual  
1113 510(k) and CLIA Waiver by Application. The RWD from the patient registry supplemented data  
1114 from a more traditional clinical study and from peer-reviewed literature. Following Agency  
1115 review, FDA considered the RWE to be valid scientific evidence; the RWD was fit-for-purpose  
1116 and potential sources of bias were minimized. The RWD was fit-for-purpose as it included  
1117 appropriate data elements that were captured in the data and was appropriately linked to the  
1118 specific assay in question (e.g., coding scheme using LOINC or Systematized Nomenclature of  
1119 Medicine Clinical Terms [SNOMED CT]) in addition to information about the setting in which  
1120 the assay was performed and the operators who performed the test.<sup>47</sup> Additionally, it was  
1121 important that the sponsor ensured that the DI, patient identifier (ensuring appropriate patient  
1122 population and rationale for any exclusions (e.g., vaccination status)), relevant demographic and  
1123 clinical information, and their interrelationships were available in a single database or commonly  
1124 available RWD sources. In this example, the sponsor accounted for the use of different  
1125 instruments in generating the results as well as the use of different controls that make it difficult  
1126 to show equivalent performance or understand the comparator used.

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<sup>46</sup> For more information on FDA’s emergency use authorities under section 564 of the FD&C Act, see FDA’s guidance “Emergency Use Authorization of Medical Products and Related Authorities,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities>

<sup>47</sup> For more information on the Dual 510(k) and CLIA Waiver by Application pathway, see FDA’s guidance, [Recommendations for Dual 510\(k\) and CLIA Waiver by Application Studies](#).