SPE's official response to the FDA's public consultation on the draft guidance for industry on use of electronic health records (EHR) and medical claims to support regulatory decisions on drug and biological products

Type of comment	Section	Line Number	Comment	Suggested Change:
			These comments are submitted on behalf of and are endorsed by the International Society for Pharmacoepidemiology (ISPE). For questions, please contact cindy.girman@cerobs.com, on behalf of the RWE and Regulatory Decisions working group of the ISPE RWE Task Force..	**Note: Thanks to the RWE and Regulatory Decisions group for drafting and comments well as ISPE membership and Board for their review and comment.**
	Preamble to comments	Intro to comments	**The FDA Draft Guidance on RWD: Use of EHR and medical claims to support regulatory decisions for drug and biological products is a giant step forward to being able to use RWD for effectiveness and safety of products. The guidance focuses on selection of data sources that appropriately capture the necessary study elements for the specific research question (population, outcome, exposures, confounders) and addresses validation, misclassification and missing data, as well as curation and QA/QC to demonostrate sufficiently high data quality. ISPE applauds the FDA for the release of this new draft guidance. However, there are several areas that recommend unprecedented high hurdles for data quality and validation that are not required for RCTs despite such RCT data potentially stemming from the same data source. ISPE respectfully submits these comments and suggestions for the FDA consideration as the draft guidance is revised.**	**none**
MAJOR COMMENTS				
Major	III	All	The focus of data source selection on whether the study elements of PICOTS (population, intervention or treatment, comparator, outcomes, timing and setting) + covariates are adequate for the study (fit-for-purpose) is appropriate. However, not every covariate is equally important to the PICO elements and to the research question or regulatory decision. The guidance in places implies that all covariates should be 'validated' which is impractical for any database not fully owned and curated by the Sponsor. Further, this is not required for most RCTs.	**Emphasize that Sponsors should <u>justify the adequacy</u> of data (fit-for-purpose) to define each element of the study question (population, treatment and comparator, outcome, covariates) <u>critical to the study question</u>. Acknowledge that not all covariates potentially available and used in for example, propensity scores, are of equal priority in strength of relationship to outcome. Also, acknowledge that all data sources and research studies will have some limitations; the limitations should be acknowledged and sensitivity analyses or quantitative bias analysis should be included to support the robustness of the findings to realistic proportions of inaccuracies or misclassifications.**
Major	III	99-100 and several other places	The process for Sponsors to seek input from the FDA medical division before study conduct is unclear in terms of what type of meeting should be requested or whether this would be a SPA	**Explicitly state what process should be followed to seek input from the medical review division on use of RWD to address specific effectiveness or safety research questions. This applies to many sections of the document. See 468-469 (outcome validation approach) and 530-536 (ability to capture temporal change in database).**
Major		21-32	The draft guidance specifically states that the prior 2018 RWD Framework focused on evaluating potential use of RWE to support new indications or to help satisfy postapproval study requirements (RWE program). This new draft guidance is about use of RWE in regulatory decision-making as part of the RWE program, and the RWE Program will cover *<u>clinical studies that use RWD sources to derive RW</u>* E, with this specific draft guidance focusing on EHR and medical claims. This implies that RWE may be the source of data for approval of products, labeling changes, new indications as well as post-approval study requirements.	**Please clarify if this draft guidance covers use of RWD for FDA decision-making in drug and biological product approval in addition to new indications, labeling changes and post-approval requirements.**
Major	IV	152-156	The chances of Sponsors being able to modify EHRs for a study are minimum to nil, depending on the health system at hand.	**Acknowledge that there are other ways to collect additional patient data during routine care (besides modifying EHR) or through ePROs, recognizing that this may be the topic of another guidance. Consider breifly highlighting a couple of examples of ways to collect addtional patient data during routine care.**
Major		180-182	2. Background information about the health care system (method of diagnosis, preferred treatments for disease, degree to which such information is collected and 'validated'	**Consider changing to: 'Relevant background information about the health system use of diagnostic criteria and treatments that will have impact and relevance on the study findings should be described'**
Major		269-272	FDA recommends demonstrating whether and how data from different sources can be obtained and integrated with acceptable quality, given the potential for heterogeneity in population characteristics, clinical practices and coding across data sources	**Clarify what is meant by 'demonstrating', what type of information would be useful and that it pertains only to the specific study population and study elements critical to address the study question**
Major		444-447, 463-464, 821-823, 845-847, 888-889, 900	Complete verification of a variable of interest to minimize misclassification	**Acknowledge that this is often impractical in research databases that are not owned by the Sponsor**
Major		455-461	Understanding how potential misclassification of a variable of interest might impact the assessment of the association and interpretation of results, sponsors should consider the degree of misclassification, whether it is differential and whether it is dependent vs independent, as well as the direction of the bias	**Clarification would be useful as to what information FDA would like to see on the potential impact of misclassification and whether sensitivity analyses such as reporting findings if the misclassifcation was as high as x% would suffice; in addition, if the misclassification may introduce bias in both directions, what analyses would FDA prefer?**
Major		472-475	FDA recommends assessing the performance of operational definitions in an adequately large sample of the study population as part of the proposed study, using justified sampling methods (e.g., random sampling, stratified sampling)	**Clarify what performance characteristics are acceptable; define adequately large; also, clarify that the operational definitions pertaining to outcomes would seem to have greater priority than covariates that may not be that important, and hence should be prioritizing in assessing performance.**
Major	V.B.	545	Key variables used to select the study population should be validated	**Clarify what variables would be considered key - age and diagnosis code and/or procedure code is often used to define a population. Age and certain other variables are not typically validated. Is it the capture of a specific diagnosis or algorithm of such diagnoses and procedures? if they have been used to define populations in studies that Sentinel has done, is that sufficient? Does clinical review of the coding algorithm suffice? It has not been typical that variables used in identifying the population be validated per se unless there are issues with the capture of aspects of the definiton and this is not done for primary data collection or RCTs; instead the operational definition to identify the study population has been justified**
Major	V.C.	573-576, 656-658	The exposure definition should include information about the drug dose, formulation, strength, route, timing, frequency and duration	**Much of this information may be missing or incomplete from EHR/claims and requiring these fields could severely limit use of RWD. Clarilfy that the importance of having complete and accurate data in these fields depends on the study question. Clarify whether there a minimum set of variables that would be needed regardless of the research question.**
Major		668-694	Validation of exposure data to a reference data source	**Add acknowledgement that it is not typical to have a referent data source available with which to validate exposure unless working with linked EHR and claims (where prescription orders can be compared to prescription fills).**
Major		771	Sponsors should discuss proposed outcomes definitions with FDA review division	**Clarify process and timing**
Major		820	"FDA expects validation of the outcome variable to minimize outcome misclassification."	**It is not the process of validation that minimizes misclassification unless you are doing the validation in the study and correcting values. Validation is often the process of assessing performance of the operational definition in terms of sensitivity, specificity and predictive value. It may or not be done as part of the study. Suggest changing to read: Operational definitions of outcomes that have been shown to have good measurement properties would be expected to have lower misclassification.**
Major			Ideally through complete verification of the outcome variable, each subject is assigned an accurate value of the outcome variable to minimize outcome misclassification and improve study internal validity.	**This seems more like data verification and auditing, not so much 'validation' by looking at the performance properties of an operational defintion of outcome. Suggest clarifying the terms verification and validation everywhere used. Also, why wouldn't data verification take a risk-based monitoring approach, such that variables that have more impact on the overall results and conclusion are prioritized?**
Major		858-864	...a moderate or low PPV might warrant complete verification for all cases. When FPs and FNs are both of concern, sponsors should consider assessing all performance measures needed for QBA to evaluate the impact of misclassification on findings or take a more rigorous approach by validating the outcome for all cases and non-cases to accurately classify the outcome variable for each subject..	**Suggest clarifying that the balance of FP and FN may drive this. Undertaking an assessment of all those meeting operational definition for cases and non-cases would be impractical in large studies. In such cases, would a random sample of potential cases and non-cases suffice? The last part of the sentence should read 'verifying' not validating**
Major		888-898	performance of an operational outcome definition should be assessed in the proposed study population using a justified sampling strategy	**Earlier in the Guidance, there was reference to 'random sampling or stratified sampling'. Can FDA elaborate on their expections on the sampling? Would a random sample of the potential cases and potential non-cases suffice?**
Major		922-923	Differential misclassification might be minimized in studies in which exposure status is blinded	**In EHR and medical claims, clarify that this is only likely possible if an adjudication or central review is performed. Additionally, suggest clarifying that such minimization of differential misclassification through blinding is expected with subjective variables or complex algorithms (in which accurate classfication is inherently more difficult) and that objective, simple variables are less likely to be systematically inaccurately classified.**
Major		954-958	FDA recommends including a quantitative bias analysis in the protocol as a sensitivity analysis to demonstrate whether and how outcome misclassification might affect results	**Suggest elaborating on what sort of QBA is being sought and might be considered accepted by FDA**
Major		962-969	In US, death and cause of death are generally not included in EHR data, unless death occurs while a patient is under medical care	**Death is available in some claims data sources (e.g., Medicare) but may not be available in other sources. Even when death is available, cause of death may not be known; Clarify that medical claims may be another source of data if the National Death Index or other vital statistics databases are not recent enough or would take too long to link.**
Major		976-979	For studies assessing fatal outcomes, excluding patients who appear to be lost to follow-up at any time after exposure is likely to create bias. These patients should be included in searches of vital statistics systems to see if their absence (disenrollment) from the system is due to death and it may be necessary to classify their deaths as outcomes of interest in the absence of data to the contrary	**To clarify, it is being suggested that sensitivity analyses including such patients as death if it cannot be verified that the patient is alive? Also, should any outcome that could possibly result in death, directly or indirectly, be evaluated for vital status? Acknowledge that death is not typically verified in this way for RCTs, despite the information on death potentially stemming from the same EHR source.**
Major	V.E.	1001-1003	FDA recommends considering potential linkages with other data sources or additional data collection to expand the capture of important confounders that are unmeasured or imperfectly measured	**Clarify if QBA and sensitivity analyses could be useful to address potential unmeasured confounders, including adjusting for confounding using an external data source (Stürmer 2007) instead of linking**
Major		1007-10014	Potential for effect modification by individuals by demographics or pertinent comorbidities should be examined in the study, and relevant effect modifiers should be available in the chosen data.	**Clarify whether sensitivity analyses similar to above could be applied if effect modifiers such as race/ethnicity were not available**
Major			In validating operational definitions that are medical events/procedures or exposures, the same principles apply as validating outcomes or validating exposures	**Please clarify that this statement refers mainly to the critical confounders and effect modifiers that would be crucial to interpretation of the results (e.g., could change the results if accounted for). Also please comment on whether external data sources can be used to calibrate or apply sensitivity analyses to understand the impact on interpretation, if such confounders or effect modifiers were not obtainable.**
Major	VI.	1067-1068	...verifying data against its original source	**Acknowledge that with electronic databases, particularly for EHR, the database may be the only source as it is that source that is what is often used for clinical care. Additionally, the closed (adjudicated) billing data (i.e., claims) are often considered the original source for pharmacy dispensing of medications.**
Major		1073-1079	The study protocol and analysis plan should specify the data provenance (curation and transformation procedures used throughout the data life cycle) and describe how these procedures could affect data integrity and the overall validity of the study. Below are points for consideration when examining data at each step in the data life cycle, including (A) characterizing the data with respect to completeness, conformance, and plausibility of data values, (B) documenting the QA/QC plan that includes transformation processes; and (C) defining a set of procedures for ensuring data integrity.	**Acknowledge that sponsors are often retrieving data from a licensed database and may not have access this information from the vendor/data owner. Consider requesting documentation on overall curation and QA/QC procedures from the large claims and EHR database vendors so that FDA has access to it.**
Major		1092-1099	Methods for data retrieval and processes to minimize missing data in extraction; data quality checks in data captured at point of care for core data elements. Provenance of core data elements to allow tracking of these elements back to their respective points of origin, with clear documentation of modifications that may have occurred	**Acknowledge that sponsors are often retrieving data from a licensed database or a data cut from a vendor and would not have access to the original database from the vendor, nor access to point of care data.**
Major		1087-1088	Documentation and automated standardized data quality reports	**It would be extremely useful to have a template document which outlines how FDA would like to receive all of this documentation. In addition, it should be acknowledged that some of the information requested is held at the data vendor and may not be obtainable**
Major		1104-1123	Request for changes and corrections and changes in coding practices etc	**Clarify that the changes and corrections refer to the key study elements and not to the variables and coding not pertinent to study**

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Major		1159-1160	De-identification of patient records and ability to re-identify unique patients in original data source without losing traceability	Acknowledge that this is done not by the Sponsor but by the data holder/owner/vendor
Major		1245	...submitted programs	This reference to submitted programs suggests that analytic datasets should be submitted. To be clarified. Sponsors may not have access to analytic datasets and/or may not be able to share analytic datasets per data license agreements.
Major		All		A RWD template protocol that covers the considerations laid out in this draft Guidance, including appendices with computable phenotype definitions (operational definitions), would be extremely helpful
MINOR COMMENTS				
Minor	II	83-90	The draft guidance specifies "pharmacoepidemiology safety studies" in reference to the 2013 guidance in line 83 and "clinical studies" as the focus of this guidance in line 90. It is unclear whether this guidance would also apply to pharmacoepidemiology safety studies (as a subset of clinical studies) or whether pharmacoepidemiology safety studies are considered part of the clinical studies efforts. Additionally, it is unclear whether all aspects of this guidance are equally applicable to premarket and post-approval studies.	Please clarify the extent to which this draft guidance covers pharmacoepidmiology safety studies and post-approval studies. Suggest highlighting situations in which considerations may differ across clinical studies including data from EHR and claims.
Minor		165-174	Distinction between what claims may provide and what EHR typically provides is appropriate here.	Consider adding: "Commercially insured claims data will often be lacking demographics and SES beyond age and gender, and may capture only specific age ranges in the U.S. (Medicare), only lower income (Medicaid) or only commercially insured (most licensed claims databases) through employees with potential of supplemental insurance to Medicare. The limitations of the data source on generalizability to the indicated population should be acknowledged in the protocol".
Minor		184-185	3. 'A description of <all> prescribing and use practices in the health care system (if available) including for approved indications, formulations and doses' is beyond the scope of the protocol.	Consider changing to: A description of any available information on prescribing practices that may impact interpretation of the study findings or feasibility of the study in the data source (e.g., stepped therapy, prior authorizations, formulary restrictions) should be provided.
Minor		187-188	For ex-US data sources in the 'explanation of how all of these factors might affect generalizability to the US'	Please clarify that this is a qualitative explanation about how the generalizability may apply
Minor		196-199	Sponsors should demonstrate that each data source contains the detail and completeness needed to capture the study populations, exposures, key covariates, outcomes of interest and other parameters relevant to the study question and design	Clarify what is meant by 'demonstrate' - is this merely a description of what is contained in the database? If so, consider changing to 'describe and justify'
Minor		226-229	Information should be provided about the distribution of length of follow-up in the data source ...	Clarify that this is average follow-up overall in data source, and not for the specific population being studied. As this is part of justification of the data source at the protocol stage, this information is often unavailable at this point for the specific population of interest unless a formal feasibility assessment is done.
		363-365	The computable phenotype definition, composed of data elements and phenotype algorithm, should be described in the protocol and study report and should be available in a computer-processible format.	The computable phenotype definition, composed of 'standardized and mapped' data elements and phenotype algorithm, if applicable, should be be described in the protocol and study report and should be available in a computer-processible forma
Minor	IV.B.	386-393	FDA notes that various methods can be used to extract data from notes or other unstructured fields of EHR and those with significant human-aided curation and decisions may inject additional variability and quality considerations	Clarify if the process for extracting data from unstructured fields (manual, AI or NLP) should be justified in terms of quality and validity if the extraction is intended to identify or supplement outcomes (as is suggested later in draft guidance)
Minor	IV.C.	397-422	FDA highlights two broad cases in which information may be absent from the data sources: missing when intended to be collected, and absent because it was not intended to be collected in EHR and claims. Four circumstances are provided within an example.	Section should acknowledge that there is not alway a way to tell the difference between these two broad categories by using the data source. For example, presence of a lab order in a claims dataset would indicate that the test was ordered, but lack of results in claims data would not delineate between the test not being conducted and results not being captured if the claims data did not intend to collect and curate that data.
Minor		413-414	....It may be possible to identify a variable(s) that is a proxy for the missing data	Clarify what justifies a proxy variable - if it has face validity (seems reasonable from a qualitative perspective) or if a variable moderately correlates with the missing variable in an another dataset, does that consitute justification?
Minor	IV.D.	426-431	Conceptual definition should reflect the current medical and scientific thinking about a variable of interest	It might help the reader to clarify that for population, treatments, and outcome, this is the definition of the variable that might be included in the research objective/hypothesis for the study
Minor		433-439	Operational definition to allow extracting the most complete and accurate data	This is the definition that might be included in the details of the protocol where the study population, treatments, outcomes and other covariates are defined explicitly, typically using coding algorithms of diagnoses, procedures and other available data
Minor		475-477, 890-89	If an operational definition from a prior study is being used, the operational definitions should be assessed in the same data source and in a similar study population	Suggest changing 'same data source' to 'similar data source'. If the operational definition has been shown to perform well in one claims database, it should perform comparably in another claims database as long as the study populations do not differ widely
Minor	V.A.	512-517	FDA recommends clearly defining various time periods pertinent to the study design in the protocol....	Consider adding a 'washout' time period (e.g., in a new user design) to the examples listed
Minor		568-584, 747-771	Exposure and outcome are defined in section V.C. and V.D. However, these terms are used throughout the guidance.	Suggest providing defintions of population, exposure, outcome, covariate, confounder, and effect modifier early in the guidance document.
Minor			...additional studies conducted in the 'same population' or published in the literature....	Change 'same population' to 'comparable population and clarify if 'or published in the literature' is the correct terminology. Is the intent to mean whether or not published?
Minor		704-705	...where it may be necessary to obtain the patient's weight and describe the dose within weight categories	Clarify that the need for weight in studies of products that dose by weight, is driven by the study question. Not all studies of such products would necessarily require weight
Minor		709-725	Selecting a comparator is an essential part of a study -	This section seems out of place.
Minor	V.D.	764-767	..., proxy measures or multi-component definitions may need to be explored and their use justified	Clarify what information would need to be provided to justify a proxy measure and what is meant by multi-
Minor		944	such as validating the outcome variable for all potential cases or non-cases	Change 'validating' to 'verifying'