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Panelists:

- **Laurence Djatche, PharmD**, Health Economics and Outcomes Research Post-Doctoral Fellow, College of Population Health, Thomas Jefferson University, Philadelphia, PA, USA
- **Nneka C. Onwudiwe, PhD, PharmD, MBA**, PRO/PE Scientific Reviewer, Government, Silver Spring, MD, USA
- **Samuel Wilson, PhD**, Associate Director-Statistics, Astellas Pharmaceuticals US, Inc., Northbrook, IL, USA
- **Helene Karcher, PhD**, Managing Vice-President and Global Head of Modeling, Analytica Laser, Basel, Switzerland
- **Judith J. Stephenson, SB, SM**, Principal Scientist, Survey Research, HealthCore, Inc., Wilmington, DE, USA
Agenda for today’s forum:

• **Introduction to missingness**
  • What does it mean?
  • Categories of missing data (MCAR, MNAR, etc.)
  • Methods of dealing with missing data

• **Case examples**
  • *Natural disease progression*
    • Filling missness with RWD
  • *Real world studies*
    • Types of real world observational studies
    • Threats to the validity of real world data

• **21st Century Cures Act**
  • Missing Data and the regulatory concerns

Missing Data: A Regulatory Perspective

Nneka Onwudiwe, PharmD, PhD, MBA
Professional Biography

Dr. Nueka C. Onwudiwe
PRO/PE Scientific Reviewer

Nueka C. Onwudiwe, PhD, PharmD, MBA, received her doctorate in Pharmacy (PharmD) from the University of Maryland School of Pharmacy, PhD in Health Services Research with a specialization in Pharmacoeconomics from the University of Maryland School of Pharmacy, and a MBA (Honors) from the University of Baltimore. In addition, she received an honor of Phi Chi in Pharmacy in 2002 and an honor of Beta Gamma Sigma in Business Administration in 2012.

Dr. Onwudiwe is a Patient-reported outcomes (PRO) and Pharmacoeconomics (PE) Regulatory Review Officer at the Food and Drug Administration (FDA). Dr. Onwudiwe is the technical expert and point of contact in the review of PRO, PE, and other type of claims in prescription drug promotion for the Division of Advertising and Promotion Review II (DAPR II) within the Office of Prescription Drug Promotion.

Dr. Onwudiwe teaches Comparative Effectiveness Research (CER) & Pharmacoeconomics at the University of Maryland School of Pharmacy. Dr. Onwudiwe has received several awards and accolades over the years. She has received funding as a Principal Investigator from NIH/NHLBI. Dr. Onwudiwe currently serves on the Food and Drug Law Institute’s (FDLI) Publications Peer Review Committee and as a Co-Chair for the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Workshop Review Committee, as well as a member of the ISPOR Value Assessment Frameworks Stakeholder Advisory Panel.

Dr. Onwudiwe has served on several ISPOR Scientific and Health Policy Working Groups (Task Forces and Special Interest Groups) that have developed products and tools used by decision makers and researchers around the world. She is currently serving on the Value Assessment of Medical Device Special Interest Group and Statistical Methods in Health Economics and Outcomes Research Special Interest Group. In addition to this work, Dr. Onwudiwe has presented at various professional conferences and published in several peer-reviewed journals such as Value in Health Regional Issues, Spine, Journal of the American Medical Association (JAMA), Obesity, Oncologist, Cancer Medicine, and Ethnicity and Disease.

Dr. Onwudiwe holds a license in pharmacy and practices as pharmacist in the community providing medication therapy management (MTM) and other services.

Disclaimer

“The views expressed in this presentation are those of the speaker, who is not here as an official FDA representative. Therefore, nothing in this presentation should be construed to represent FDA’s views or policies.”
Abstract

Title: HANDLING MISSING VALUES IN REAL-WORLD DATA (RWD): ARE THERE CHALLENGES FOR REGULATORY DECISIONS FOR MEDICAL PRODUCTS?

Interactive Audience Element: The panel will discuss the best approach and provide recommendations for conduct and reporting, and allow the audience to participate in the discussion and provide feedback through questions posed to attendees.

PURPOSE: Section 3022 of the 21st Century Cures Act directs FDA to evaluate and issue guidance on the use of real-world evidence to support approval of a drug or to satisfy post-approval study requirements. However, the problem of handling missing values in real-world healthcare datasets is not completely solved. Namely, the flexibility in methods to handle missing data in analyses and the assumptions made about the data can lead to different results and/or introduce biased estimates. Are there challenges ahead?

DESCRIPTION: Missing data can represent a potential source of bias and a substantial loss of precision and power in randomized trials and observational studies. Missing data in healthcare datasets such as claims, registries, and electronic medical records can present unique challenges. Missing data is generally categorized as missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). The credibility of the analysis will depend on the amount of missing data, reasons for missingness (e.g., outcome data, baseline covariates), assumptions made about the data, and the methods used to handle missing data. One approach to handle the missing values is to conduct a sensitivity analysis to assess the robustness of results produced using different algorithms. There are two main methods for conducting sensitivity analysis: complete case analysis and imputation methods. Complete case analysis only includes cases with complete data, which can possibly result in less precision and often biased estimates. There are various imputation techniques for missing data such as last observation carried forward (LOCF), multiple imputation, regression imputation, etc. Nevertheless, complete case analysis is considered the most common approach to handling missing data. ISPOR’s Statistical Methods in Health Economics and Outcomes Research Special Interest Group has set out to provide statistical leadership for strengthening the use of appropriate statistical methodology in health economics and outcomes research and improve the analytic techniques used in real-world data analysis. This forum will discuss the best possible methods for handling missing data and potential drawbacks from their perspectives, depending on the context of the analysis. The speakers will also include their experiences in handling missing data, and provide recommendations for conduct and reporting. The presentations will focus specifically on the reasons for missingness (e.g., outcome data, baseline covariates), assumptions made about the data, the methods used to handle missing data, and the intended use of the results. The speakers will address how incorrect assumptions underlying the mathematical model used to fix the missingness can lead to biased estimates and eventually to misleading recommendations. Finally, speakers will discuss the regulatory impact and challenges when informing regulatory decisions related to approval and promotion.

Validity: Experimental vs. Observational

<table>
<thead>
<tr>
<th></th>
<th>Experimental</th>
<th>Observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomized Control Trial</td>
<td>Cross-sectional</td>
</tr>
<tr>
<td>Study population</td>
<td>Highly selected population; highly controlled environment</td>
<td>Diverse population observed in a range of settings</td>
</tr>
<tr>
<td>Directionality</td>
<td>Exposure is assigned before outcome is ascertained</td>
<td>Exposure and outcome ascertained simultaneously</td>
</tr>
<tr>
<td>Primary Use</td>
<td>Demonstrating efficacy of an intervention</td>
<td>Screening hypotheses; prevalence studies</td>
</tr>
<tr>
<td>Analysis</td>
<td>Straight-forward</td>
<td>Sophisticated multivariate techniques may be required to account for confounding</td>
</tr>
<tr>
<td>Internal validity</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>External validity</td>
<td>Low-Moderate</td>
<td>High</td>
</tr>
</tbody>
</table>

Carlson M & Morrison RS. Study Design, Precision, and Validity in Observational Studies
Threats to the Validity of Real World Data (RWD)

- Confounding
- Measurement error
- Selection bias
- Missing data

Introduction and Key Concepts

- Missing data can be a source of bias and result in a substantial loss of statistical power and precision
- These issues are present across both interventional and non-interventional studies
- The issue and varying guidelines of handling of missing data in clinical trials have been addressed through regulatory and GCP stakeholders to include ICH, FDA, NIH, and numerous private and peer reviewed publication sources. This is a well known issue that requires the attention of real-world and health economics analysis groups
**Missing Data Theory— Mechanisms**

\[ g_{\phi}(m|u) = \prod_{i=1}^{n} \phi^{m_i}(1-\phi)^{1-m_i}. \]

**EXAMPLE 1**

\[ g_{\phi}(m|u) = \prod_{i=1}^{n} \delta[\gamma(u_i) - \phi] - m_i, \]

where \( \gamma(a) = 1 \) if \( a \geq 0 \) and 0 otherwise; \( \delta(a) = 1 \) if \( a = 0 \) and 0 otherwise

**EXAMPLE 2**

\[ g_{\phi}(m|u) = \prod_{i=1}^{n} \delta(1-m_i) \prod_{i=n+1}^{n} \delta(m_i), \]

where \( n_i \) is the minimum \( k \) such that the function \( Q_k(u_1, \ldots, u_k) \in C \)

**EXAMPLE 3**

\[ g_{\phi}(m|u) = \begin{cases} 
\phi & \text{if } m = (1, 0), \\
(1-\phi)\gamma(u_1) & \text{if } m = (1, 1), \\
(1-\phi)(1-\gamma(u_1)) & \text{if } m = (0, 1), \\
0 & \text{if } m = (0, 0). 
\end{cases} \]

**EXAMPLE 4**

**Terminology**

- **Missingness**—the existence of missing data and the mechanism that explains the reason for the data being missing
- **Missing data mechanisms**
  - MCAR
  - MAR
  - MNAR
- **Proportion of missing data**— directly related to the quality of statistical inferences
- **Missing data occur at two levels**
  - Unit level or item level
- **Patterns of missing data**
  - Univariate, monotone, arbitrary
- **Statistical methods**
  - Direct imputation (LOCF, BOCF), MMRM, MI, weighting, etc.
- **Assumptions and patterns of missingness to determine statistical methods**
  - MCAR, MAR, MNAR
  - assumptions of analytic models
Key Concepts of Missing Data and Case Study: Informative Censoring

Samuel Wilson, PhD

Disclaimer

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Categories of Missing Data

• Missing Completely at Random (MCAR)
  • Whether or not a value is missing is unrelated to the unobserved result
  • \( P(M|Y) = P(M|Y_{\text{miss}}, Y_{\text{obs}}, \theta) = P(M|\theta); \; M = 1 \text{ if } Y \text{ is missing, and } 0 \text{ otherwise} \)
  • \( \theta \) indicates conditions of \( Y_{\text{miss}} \) (e.g., if \( \theta = \text{weight} > 120 \text{kg} \) then \( M = 1 \)) or covariate(s) in the data

• Missing at Random (MAR)
  • The occurrence of missingness is not random. However, missingness is conditionally random and not dependent on the unobserved \( Y_{\text{miss}} \).
  • \( P(M|Y) = P(M|Y_{\text{miss}}, Y_{\text{obs}}, \theta) = P(M|Y_{\text{obs}}, \theta) \)

• Missing Not at Random (MNAR)
  • Anything else (also known as Nonignorable Nonresponse)
  • Missing values depend on the value of the unobserved result
  • \( P(M|Y) \neq P(M|Y_{\text{obs}}, \theta) \)

Some Common Methods Dealing with Missing Data

• Deletion
  • Pairwise deletion
  • Listwise deletion (complete case)

• Imputation
  • “Simple” Imputation (mean, median, worst observation, last observation, etc.)
    • These assume greater information is known than is available at the time of analysis due to the imputed values being assumed as known realizations (i.e., resulting in artificially small standard errors and possibly biased p-values)
  • Partial Imputation
    • In the case of the Expectation-Maximization (EM) algorithm, estimation assumes complete data were available, while taking into account the pattern of missingness
  • Multiple Imputation and Maximum Likelihood
    • Generally considered preferable to the above as these control the information inflation limitations of simple and partial imputation
    • Generally require simulation
An Example: Informative Censoring

- A urology EMR oncology study
  - Endpoint is treatment duration (medication persistence)
  - Analysis for this is time-to-event, using product-limit estimation (Kaplan-Meier)

- Missing values for treatment discontinuation (censored values) were suspected to not be independent of the treatment duration
  - If true, this is known as Informed Censoring:
    - Censored values are related to the unobserved event time

- Informative censoring is a violation of the analysis assumptions for product-limit estimation and potentially bias parameter estimates

Example: Informative Censoring

- 69% of the study cohort had missing treatment discontinuation (censored)

- The majority of censored patients were lost-to-follow-up relatively early versus those not censored (figure below)
  - These censored patients may have had a different distribution of treatment discontinuation (i.e., censoring was related to unobserved persistence)
  - Note – this cannot be verified directly as treatment discontinuation in censored patients is unobservable
Example: Informative Censoring

Why did we believe the difference in distributions showed that the unobserved persistence was different from those that were observed?

- This was our fourth retrospective database analysis of persistence in the same indication and treatment. Results from the first three showed consistent persistence estimates, were claims based, did not have this censoring property or frequency of censoring.
- Point estimates from this study were orders of magnitude greater than our earlier studies.

Approach:

- Can we find $\theta$ such that MAR is concluded (i.e., can we condition out the suspected dependence of $M$ and $Y_{miss}$)?
- $P(M|Y) = P(M|Y_{obs}, \theta)$

Sensitivity analyses

- Let $\theta$ be the reason for censoring
  - Hypothesis: The patients who left their urology practice make up the majority of the early censored patients
  - Why would this matter?
    - Did these patients represent early progression or those with a worse prognosis and were quickly referred to oncologists?
    - This could lead to informative censoring if it led to a different distribution of persistence than those not censored (due to a different disease state at baseline).

- Censoring was reduced by 13% (from 69%)
  - Point estimates remained approximately 50% greater than previous analyses
  - Skewness of the censoring distribution remained (although reduced)
Example: Informative Censoring

- Sensitivity analyses cont.
  - Exploratory: Condition on changes to the definition of censoring using Rx gaps
    - Let $\theta$ represent the allowable gap in Rx prior to censoring
      - Double and triple the allowable gap from 30 to 60 and 90 days
      - Resulted in a 2.5 and 3.7% increase, respectively, in censoring and no noticeable change to the non-censored distribution
      - Relative differences and median persistence remained largely unchanged
      - Relative differences (below) remained unchanged also

<table>
<thead>
<tr>
<th>Treatment Gap</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first gap &gt; 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted hazard ratio (95% CI)</td>
<td>1.21</td>
<td>(1.05, 1.39)</td>
<td>0.0092</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>1.40</td>
<td>(1.15, 1.71)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Time to first gap &gt; 60 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted hazard ratio (95% CI)</td>
<td>1.18</td>
<td>(1.02, 1.37)</td>
<td>0.0230</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>1.45</td>
<td>(1.18, 1.77)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Time to first gap &gt; 90 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted hazard ratio (95% CI)</td>
<td>1.16</td>
<td>(1.00, 1.35)</td>
<td>0.0443</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>1.43</td>
<td>(1.16, 1.76)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

- Other considerations on $\theta$
  - $\theta$ based on comorbidities would have been promising, but the EMR was flawed with little information recorded at baseline
  - $\theta$ based on demographics showed the same level of inadequate control as the earlier examples with socioeconomic covariates performing better than the other variables used

- Conclusions
  - Unable to find $\theta$ such that MAR was considered valid: $P(M|Y) = P(M|Y_{obs}, \theta)$
  - This conclusion was reached through external data validation
  - Missing treatment duration values were concluded to be nonignorable (MNAR)
  - This highlighted database limitations, particular for EMRs on treatment persistence studies
  - Resulted in a decision to no longer use EMR for persistence in this indication/treatment
Regulatory Tie-in

- For RWE, FDA stresses completeness and quality of data necessary for specified analyses, including adjustment(s) for confounding factors (FDA, 2017)
  - Ensure proper consideration of completeness as a function of the data source for the outcome(s) of interest
  - Special care should be taken to ensure data is also available for proper adjustments that applies not only to adjusted analyses but, in this case, conditioning missing responses
- “Awareness of the limitations of source data and analytic approaches is fueling concern that when the term ‘real-world evidence’ is used in such contexts, the allure of analyzing existing data may lead to flawed conclusions” – Sherman et al., 2016
  - This NEJM article emphasizes FDA’s position of EMRs as a viable source of RWE
  - Special care should be taken given the position of EMRs in order to avoid inappropriate claims for label expansion/advertising/promotion
  - The example emphasizes these cautions regarding the imputation and analysis of missing data that may lead to flawed conclusions

References

Using RWD to Replace Missing Data for Regulatory Submissions

Helene Karcher, PhD

RWD to replace fully-missing data in regulatory submissions

- Context: prudent introduction of RWD into FDA/EMA submissions
- Trend on submitting RWD as part of regulatory dossiers = when there is no other option? i.e., data is fully missing?

RWD to replace missing data

- Case 1: on comparative effectiveness (e.g., in cancer and rare diseases)
- Case 2: on dynamic drug effects on long term outcomes (e.g., Alzheimer’s disease)
Case 1: how to palliate a lack of data on comparative efficacy and safety for regulatory approval?

- Case when only single-arm pivotal trials are available
  - Ethical reasons: no standard of care, off-label use of other therapies
  - Operational reasons: too few patients to recruit (very rare indications)

→ Only available information on drug efficacy and safety is an improvement from baseline for each patient
**Classical solution: use control arm of previous RCTs as historical control**

- **Historical data choice:** to fit the Pocock¹ criteria for suitability (similarity of population, geography, endpoints, standard of care..)
- **Analysis:** population adjustment technique: propensity score, matched-adjusted indirect comparison (MAIC)
- Many examples submitted to FDA/EMA
  - Secukinumb in Crohn’s disease² and Ankylosing Spondylitis³
  - Lamotrigine XT in epilepsy⁴
  - 44 indications approved by EMA, 60 by FDA⁵ in total between 1999-2014:


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**What do to when no RCT exist to use as historical control?**

**Typical situation for rare and/or very specific cancer indications**

→ Leverage RWD to fill missingness in control data and evaluate comparative efficacy
Recent FDA approvals where RWD was used as historical/external control of the pivotal single-arm study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Sponsor</th>
<th>Type of RWD submitted as historical control</th>
<th>Endpoint for comparative efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blincyto¹</td>
<td>Sub-type of acute lymphoblastic leukemia (ALL)</td>
<td>Amgen 2018</td>
<td>Medical records for 121 patients over 8 years from 14 institutions in the US, Canada, Australia</td>
<td>CR</td>
</tr>
<tr>
<td>Brineura²</td>
<td>Batten disease (CLN2)</td>
<td>BioMarin 2017</td>
<td>Disease registry of 69 children (42 included): records &amp; patient interviews</td>
<td>CLN2 rating scale (motor, language)</td>
</tr>
<tr>
<td>Bavencio³</td>
<td>Metastatic Merkel cell carcinoma</td>
<td>EMD Serono 2017</td>
<td>Electronic medical records from 686 patients (14 included) from community and academic centers</td>
<td>RECIST</td>
</tr>
<tr>
<td>Exondys 51⁴</td>
<td>Duchenne Muscular Distrophy</td>
<td>Sarepta 2016</td>
<td>2 natural disease history cohorts (Belgium &amp; Italy) of about 90 patients each (13 included)</td>
<td>6-min walking test</td>
</tr>
</tbody>
</table>

¹BLA 125557 S-005 Blincyto (blinatumomab); ²BLA 761052 Brineura (cerliponase α); ³BLA 761049 Bavencio (avelumab)
⁴NDA 206488 Exondys 51 (eteplirsen) and Mendell 2016 Ann. Neurol. 79:257-271

On the 4 examples on the previous slide:
- Thorough protocol for population selection (e.g., independant reviewers to adjudicate cases), which led to much reduced population size
- Compared endpoints with low missingness
- Missingness addressed through sensitivity analyses, and in one instance through prospective data collection
• Case 2: RWD to replace missing data on long term outcomes

Case 2: Missing data on dynamic effects of early drugs on long term outcomes.

• New therapeutic concept in Alzheimer’s disease
  - Act early
  - New compounds target pre-diagnosis, at-risk patients

• Challenge
  - Impact of early drugs can only be tested on cognition (and time to disease onset)
  - Cognition will still be “good” in the control group, even with long trial duration (5-8 years)
Drug effect on long term Alzheimer’s disease outcomes that are clinically relevant?

- Drug-induced changes on later, more severe cognitive impairment?
- Changes to functional impairment?
- Changes to behavior & time to institutionalization?

Classical endpoint surrogacy methods (with thresholds) lack power to predict changes.

Solution: use several disease registries to develop a series of dynamic models that stitch together outcomes sensitive in different parts of the disease spectrum.

Data sources
Disease registries of subjects visiting a memory clinic

E.g.: ADNI, NACC, Rush, Memento, Goeteburg...

• Solution vetted by a panel of regulatory & HTA experts last February as part of the European Roadmap consortium.
An example of such model developed on ADNI data*

**Link longitudinal decline in cognition to later decline in function**

### Cognitive decline model
- Most sensitive cognitive score in pre-symptomatic setting in ADNI
- Emax nonlinear mixed-effects model with covariates

### Functional decline model
- Functional score captured in ADNI
- Emax nonlinear mixed effects model with covariates
- Individual-level parameters from the cognitive decline model used to explain parameters of the functional model

- Use the model-derived relationship between longitudinal decline in cognition to predict decline in function for each individual, treated or not.


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**Conclusion**

We are still at the beginning of using real-world data (RWD) in regulatory submissions.

Regulators may be more likely to accept RWD when it is used to fill missingness in critical data, not obtainable from RCTs, and is of high quality, low missingness.

Two examples are:

- For comparative efficacy/safety when only single-arm trials are available
- For estimation of clinically-relevant outcomes when only earlier ones can be measured
Real world studies involve the use of real world data (RWD) that can be used in health care decision-making

- Real world data (RWD)
  - Related to patient health status and delivery of health care
  - Collected from a variety of sources

- Sources of RWD
  - Claims and billing activities
  - Medical records/electronic health records (EHRs)
  - Product and disease registries
  - Lab result databases
  - Patient and physician self-report (surveys)
  - Health-monitoring devices
Missingness occurs in different ways both within and across types of real world studies

- **Types of real world studies**
  - Retrospective claims studies
  - Cross-sectional & longitudinal survey studies
  - Medical record/EHR studies
  - Safety/epidemiology studies
  - Registries
  - **Pragmatic Control Trials (PCTs)**
  - Hybrid studies combining more than 1 study type

- **Sources of missingness**
  - Non-response/participation
  - Attrition
  - Item/variable non-response
  - Survey non-completion
  - Patient non-compliance

Missing value imputation in PCTs

- Missing data in PCTs can be a problem because real world settings cannot control things like patient compliance
- This analysis compares the accuracy of listwise data deletion (LD) and a set of widely available imputation methods: MICE, Amelia, MissForest, Hmisc, mi, and DBI
- Methods:
  - Before random missing values were included in the data, each of the imputation methods were calculated against the complete data
  - Data simulations performed in R with 200 replications across all crossed parameters below
    - Using Cholesky's decomposition in R, 3 correlation levels simulated: Low: $r=0.20$; Moderate: $r=0.50$; High: $r=0.80$
    - 3 different sample sizes per sample: 1,000, 500, 200
    - Missing value percentages: 5, 15, 25, 35, 45, 55, 65, 75
    - Each sample constructed with all variables regenerated for each sample
    - Complete sample values were computed using linear regression with continuous dependent variable and 4 continuous independent variables; only 1 independent variable was used for randomly inserting missing values
    - Values calculated and extracted for each sample: Beta coefficient for each independent variable; model R2
    - Listwise calculations for all variables calculated after random values were deleted
    - Bias data calculated by counting number of times each estimator provided over or under estimate of complete data; unbiased estimator close to 0.0
Summary of imputation methods

<table>
<thead>
<tr>
<th>METHOD</th>
<th>DESCRIPTION</th>
<th>APPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariate Imputation by Chained Equations (MICE)</td>
<td>Imputation performed by regression for all variables; value considered MAR; missing value created by examining results of multiple imputations</td>
<td>Can be used to impute continuous and binary data</td>
</tr>
<tr>
<td>Amelia</td>
<td>Multiple imputation method based on a common bootstrap over the missing values</td>
<td>Only used to impute variables that are normally distributed at the continuous level</td>
</tr>
<tr>
<td>MissForest</td>
<td>Applies forest algorithm; non-parametric imputation method; constructs random forest model using observed values of available data</td>
<td>Can be used to impute continuous and categorical data</td>
</tr>
<tr>
<td>Harrell Miscellaneous (Hmisc)</td>
<td>Multiple options for imputation including mean or minimum/maximum values</td>
<td>Can be used to impute continuous and binary data</td>
</tr>
<tr>
<td>Multiple Imputation (mi)</td>
<td>Uses Bayesian regression; detects and corrects for collinearity between variables and adds error to arrive at the imputed variable</td>
<td>Can be used to impute continuous and binary with multiple levels as well as ordinal/categorical data</td>
</tr>
<tr>
<td>Distributional Based Imputation (DBI)</td>
<td>Uses univariate approach and generates distribution of values based on existing mean and SD for non-missing values; substitution made at random which adds error for model tested</td>
<td>Can be used to impute continuous data only; has been shown to be more accurate than mean-based imputation</td>
</tr>
</tbody>
</table>

Model R2

- Lower the correlation between variables, worse estimates of R2
- Smaller the sample size, worse estimates of R2
- Best estimators of R2: DBI, mi and Hmisc
- Worst estimators of R2: LD, MissForest and Amelia
**Independent variable Beta (top row) and Standard Error (bottom row) pooled over correlation level, by sample size and percent of values missing**

- Smaller the sample size, worse estimates of $B$ and SE-$B$
- Best estimators of $B$: LD, mi and Hmisc
- Worst estimators of $B$: MissForest, MICE and DBI
- Best estimators of SE-$B$: MICE, Amelia, Hmisc, mi and DBI
- Worst estimators of SE-$B$: LD and MissForest

**R-Square Bias Estimates pooled by correlation level, sample size and percent of values missing**

- Results are for all ($n=14,400$) simulations combined
- 3 estimators demonstrated low levels of bias for $R^2$: LD, Amelia and Hmisc
- 4 estimators demonstrated high levels of bias for $R^2$: MICE, mi, and DBI underestimated $R^2$ and Miss2sForest overestimated $R^2$
Conclusions

• The following recommendations are based on which value from a linear regression the researcher wants to be more accurate with low levels of bias
  – Beta coefficient for variable with missing values: LD or Hmisc
  – R2 for the model: mi, DBI or MICE
  – Least bias of R2 estimate: LD, Amelia or Hmisc

• In general, best overall method for all imputation methods appears to be Hmisc or DBI

• Ultimately the method used depends on the needs of the research
Section 3022: Real World Evidence (RWE)

SEC. 3022. REAL WORLD EVIDENCE.

Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by inserting after section 565(k) (21 U.S.C. 355(k)) the following:

"SEC. 3022. REAL WORLD EVIDENCE.

(a) In General.—The Secretary shall establish a program to evaluate the potential use of real world evidence—

(1) to help to support the approval of a new indication for a drug approved under section 505(a); and

(2) to help to support or satisfy postapproval study requirements.

(b) Real World Evidence Defined.—In this section, the term 'real world evidence' means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.

(c) Program Framework.—In not later than 2 years after the date of enactment of the 21st Century Cures Act, the Secretary shall establish a framework for implementation of the program under this section.

The program shall include information describing—

(A) the sources of real world evidence, including ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities;

(B) the gaps in data collection activities;

(C) the standards and methodologies for collection and analysis of real world evidence; and

(D) the priority areas, remaining challenges, and potential pilot opportunities that the program established under this section will address.

(3) Consultation.—

(A) IN GENERAL.—In developing the program framework under this subsection, the Secretary shall consult with regulated industry, academia, medical professional organizations, representatives of patient advocacy organizations, consumer organizations, disease research foundations, and other interested parties.

(B) Process.—The consultation under subparagraph (A) may be carried out through approaches such as—

(i) a public-private partnership with the entities described in such subparagraph in which the Secretary may participate;

(ii) a contract, grant, or other arrangement, as the Secretary determines appropriate, with such a partnership or an independent research organization; or

(iii) public workshops with the entities described in such subparagraph.

TITLE III—DEVELOPMENT

Subtitle A—Patient-Focused Drug Development

Sec. 3001. Patient experience data.
Sec. 3002. Patient-focused drug development guidance.
Sec. 3003. Streamlining patient input.
Sec. 3004. Report on patient experience drug development.

Subtitle B—Advancing New Drug Therapies

Sec. 3011. Qualification of drug development biom.
Sec. 3012. Targeted drugs for rare diseases.
Sec. 3013. Reauthorization of program to encourage treatments for rare pediatric diseases.
Sec. 3014. GAO study of priority review voucher programs.
Sec. 3015. Amendments to the Orphan Drug grants.
Sec. 3016. Grants for studying continuous drug manufacturing.

Subtitle C—Modern Trial Design and Evidence Development

Sec. 3021. Need clinical trial designs.
Sec. 3022. Real world evidence.
Sec. 3023. Protection of human research subjects.
Sec. 3024. Informed consent waiver or alteration for clinical investigations.

Subtitle D—Patient Access to Therapies and Information

Sec. 3031. Summary level review.
Sec. 3032. Expanded access policy.
Sec. 3033. Accelerated approval for regenerative advanced therapies.
Sec. 3034. Guidance regarding devices used in the recovery, isolation, or delivery of regenerative advanced therapies.
Sec. 3035. Report on regenerative advanced therapies.
Sec. 3036. Standards for regenerative medicine and regenerative advanced therapies.
Sec. 3037. Health care economic information.
Sec. 3038. Combination product innovation.
Section 3022: RWE

(4) PROGRAM IMPLEMENTATION.—The Secretary shall, not later than 2 years after the date of enactment of the 21st Century Cures Act and in accordance with the framework established under subsection (c), implement the program to evaluate the potential use of real world evidence.

(b) GUIDANCE FOR INDUSTRY.—The Secretary shall—

(1) utilize the program established under subsection (a), its activities, and any subsequent pilots or written reports, to inform a guidance for industry on—

(A) the circumstances under which sponsors of drugs and the Secretary may rely on real world evidence for the purposes described in paragraphs (1) and (2) of subsection (b); and

(B) the appropriate standards and methodologies for collection and analysis of real world evidence submitted for such purposes;

(2) not later than 5 years after the date of enactment of the 21st Century Cures Act, issue draft guidance for industry as described in paragraph (1), and

(3) not later than 18 months after the close of the public comment period for the draft guidance described in paragraph (2), issue revised draft guidance or final guidance.

(6) RULES OF CONSTRUCTION.—

(1) IN GENERAL.—Subject to paragraph (2), nothing in this section prohibits the Secretary from using real world evidence for purposes not specified in this section, provided the Secretary determines that sufficient basis exists for any such repurposed use.

(2) STANDARDS OF EVIDENCE AND SECRETARY’S AUTHORITY.—This section shall not be construed to alter—

(A) the standards of evidence under—

(i) subsection (c) or (d) of section 505, including the substantial equivalence standard in such subsection (d); or

(b) Guidance for Industry and Food and Drug Administration Staff

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

This guidance documents the Food and Drug Administration’s (FDA’s) current thinking on the use of real-world evidence (RWE) in FDA’s regulatory decision-making for medical devices. It is intended to provide FDA staff and industry stakeholders with the basis for FDA’s current thinking on the use of RWE in the context of its regulatory decision-making. The guidance addresses the use of RWE in various stages of the regulatory process, including premarket and postmarket decision-making. It also includes considerations for the use of RWE in different types of studies and the evaluation of the quality and reliability of RWE. The guidance serves as a framework for FDA staff to use when evaluating RWE and provides guidance for industry on how to support regulatory decision-making with RWE.

Introduction and Scope

The FDA is issuing this guidance to clarify how it evaluates real-world data to determine whether it is sufficient for generating the type of real-world evidence (RWE) that can be used in FDA’s regulatory decision-making for medical devices. This guidance is applicable to all medical devices, as that term is defined under section 301(k) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), including software that meets the definition of a device.

Real-World Evidence (RWE) is defined as data relating to real world use or outcomes collected from a variety of sources. Examples of RWE include data derived from clinical trials, registries, and administrative databases. RWE can be used to support the safety and effectiveness of medical devices and to inform postmarket surveillance.

RWE is defined as evidence not obtained through traditional randomized controlled trials (RCTs) but derived from clinical trials, registries, or other non-traditional settings. RWE can be used to support the approval of medical devices and to inform postmarket surveillance.

The draft of this document was issued on July 27, 2016. For questions about this document, contact the Office of Science and Research (OSR) at 301-443-8250 or visit the FDA website.

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

Guidance for Industry and Food and Drug Administration Staff


The draft of this document was issued on July 27, 2016.

For questions about this document reporting CDRH regulated devices, contact the Office of Science and Research (OSR) at 301-443-8250 or visit the FDA website.
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

I. Introduction and Scope

FDA is issuing this guidance to clarify how we evaluate real-world data to determine whether it is sufficient for generating the types of real-world evidence that can be used in FDA regulatory decision-making for medical devices. This guidance is applicable to all devices, as the term is defined under section 201(k)(7) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), including software that meets the definition of a device.

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 include data derived from electronic health records (EHRs), claims and billing data, data from product, design, and finance registries, patient-generated data including in-home use settings, and data derived from other sources that can inform on health status, such as mobile devices. RWD sources (i.e., registries, collections of EHRs, and administrative and healthcare claims databases) can be used as data collections and analysis infrastructure to support evidence types of real designs, including, but not limited to, randomized trials, such as large single, pragmatic clinical trials, and observational studies (perspective and/or prospective).

Real-World Evidence (RWE) is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.
A. Relevance

The relevance of EWD, EWD source, and recalculation analysis is assessed by evaluating several factors as outlined below. These factors can help determine if the data adequately addresses the applicable regulatory question or requirement, in particular, the question about whether the use of EWD is sufficient to support the EWD data. Questions about whether the use of EWD is sufficient to support the EWD data should be considered when evaluating whether specific EWD is sufficient to support the EWD data.

Since EWD sources are usually developed for non-regulatory purposes (e.g., to document care in the case of DSSR), it is unclear whether the individual data elements contained within an existing EWD source are sufficient to be used for a regulatory purpose. The data should be accurate, complete, and appropriate to address the question at hand (i.e., data adequacy). The need for recalculation or adjustment of specific outcomes or interests (e.g., weeds or average yield) at the patient management level may also be assessed. For analysis and interpretation of EWD, it is important to have a pre-defined scenario set of data elements, a consistent data definitions framework, data quality criteria, and pre-specified data analysis methods. In assessing the relevance of EWD, the FDA will also consider, if encountered, the ability to supplement the available EWD through linkage with other data sources to provide additional or confirmatory data, e.g., with EWD and/or administrative claims data.

Important factors for the FDA to determine if the EWD are suitable for regulatory use include:

- The EWD contain sufficient detail to capture the use of the device, sequence of events, and the outcomes of interest in the appropriate population.
- The data elements available for analysis are capable of addressing the specific question with valid and appropriate analytical methods applied (i.e., the data are statistically sound and conceptually analyzed).
- The EWD and SWD provide interpretable and meaningful clinical/clinical findings. Important considerations for the assessment of these factors include:

  - A strong evidence base from the medical literature on the EWD.
  - A strong evidence base from the medical literature on the EWD.
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Methods for Handling Missing Data in the Design Stage

Table 1. Eight Ideas for Limiting Missing Data in the Design of Clinical Trials.

Target a population that is not adequately served by current treatments and hence has an incentive to remain in the study.
Include a run-in period in which all patients are assigned to the active treatment, after which only those who tolerated and adhered to the therapy undergo randomization.
Allow a flexible treatment regimen that accommodates individual differences in efficacy and side effects in order to reduce the dropout rate because of a lack of efficacy or tolerability.
Consider add-on designs, in which a study treatment is added to an existing treatment, typically with a different mechanism of action known to be effective in previous studies.
Shorten the follow-up period for the primary outcome.
Allow the use of rescue medications that are designated as components of a treatment regimen in the study protocol.
For assessment of long-term efficacy (which is associated with an increased dropout rate), consider a randomized withdrawal design, in which only participants who had already received a study treatment without dropping out under randomization to continue to receive the treatment or switch to placebo.
Avoid outcome measures that are likely to lead to substantial missing data. In some cases, it may be appropriate to consider the time until the use of a rescue treatment as an outcome measure or the discontinuation of a study treatment as a form of treatment failure.

Little RJ et al. The Prevention and Treatment of Missing Data in Clinical Trials

Methods for Handling Missing Data

<table>
<thead>
<tr>
<th>Statistical method for handling missing data†</th>
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<tbody>
<tr>
<td>Method not stated</td>
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<tr>
<td>Complete-case analysis assumed</td>
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<td>Complete-case analysis</td>
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<tr>
<td>Unweighted</td>
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<tr>
<td>Exclude participants with missing data at any repeated waves of exposure</td>
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<tr>
<td>Exclude participant data record for waves of data collection with missing exposure data††</td>
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<tr>
<td>Missing Indicator Method</td>
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<td>Mean value substitution</td>
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<tr>
<td>Last Observation Carried-Forward</td>
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<tr>
<td>Multiple Imputation</td>
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<tr>
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<tr>
<td>Indicated which variables were included in the imputation model</td>
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<tr>
<td>Compared results from multiple imputation with complete case analysis</td>
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</tr>
<tr>
<td>Performed a sensitivity analysis under different assumptions for missing data</td>
<td>4</td>
</tr>
<tr>
<td>Fully Bayesian Model</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Karahalios A et al. A review of the reporting and handling of missing data in cohort studies with repeated assessment of exposure measures
• Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified.

• Parametric models in general, and random effects models in particular, should be used with caution, with all their assumptions clearly spelled out and justified. Models relying on parametric assumptions should be accompanied by goodness-of-fit procedures.

• For inverse probability weighting and maximum likelihood methods, this analysis can be accomplished by appropriate computation of standard errors, using either asymptotic results or the bootstrap.

• Weighted generalized estimating equations methods should be more widely used in settings when missing at random can be well justified and a stable weight model can be determined, as a possibly useful alternative to parametric modeling.

• Sensitivity analyses should be part of the primary reporting of findings from clinical trials. Examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting.

Case Study Example

• Registry for drug X, an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:
  - 30 kg/m² or greater (obese) (1)
  - 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition

• The registry collected measures of clinical effectiveness outcomes, patient-reported outcomes, and safety outcomes.

• Measures of clinical effectiveness was weight loss at 1 year, which was assessed by percent of patients achieving greater than or equal to 5% weight loss, percent of patients achieving greater than or equal to 10% weight loss, and mean weight change.

• Loss to follow-up and refusal to continue participation occurred more with drug X. In the clinical study, 9.4% of patients treated with drug X prematurely discontinued treatment due to adverse reactions, compared with 5.7% of drug Y-treated patients. The most common adverse reactions leading to discontinuation more often among drug X treated patients than drug Y were headache (2.1% vs. 0.9%), dry mouth (0.9% vs. 0.4%) and dizziness (0.9% vs. 0.3%).
## Recommendations

- If applicable, document when losses to follow-up occurred and possibly collect important information about why patients left the study
- Report on the amount of missing data
  - Indicate number of participants with missing
  - Distributions of key exposure and outcome variables in different groups
- Determine a plausible assumption about the missing data
- If possible, avoid the use of single-valued imputation methods
- Conduct a sensitivity analysis

## Conclusions

- Patients who are lost to follow-up are likely to be different from completers
- Loss to follow-up information can decrease statistical power and threaten the validity of registry data
- Missing data can limit the ability to draw inferences and cause bias in the estimation of the estimand
- With regard to decisions about the treatment benefit in a regulatory context, failure to properly account for missingness could lead to incorrect inferences about efficacy or safety
- In terms of promotion, it may be difficult to characterize the safety profile with a "well tolerated" drug claim
  - Recommend presenting the adverse events factually
  - Well-tolerated is a patient’s subjective judgment about a drug’s adverse reaction profile
  - Avoid false or misleading claims
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