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

ISPOR Special Interest Group: Statistical Methods in HEOR

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2

Agenda Review

Laurence Djatche, PharmD

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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
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4

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

5

Missing Data: A Regulatory Perspective

Nneka Onwudiwe, PharmD, PhD, MBA

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Professional Biography

Dr. Nneka C. Onwudiwe
PRO/PE Scientific Reviewer

Nneka 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 Rho 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.

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Disclaimer

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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 complete case analysis. This approach, however, assumes that the missing data are MCAR and 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, possible percentage of missing values, 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.

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Validity: Experimental vs. Observational

TABLE 2. COMPARISON OF EXPERIMENTAL AND OBSERVATIONAL STUDY DESIGNS[4–6]

	Experimental	*Observational*		
Study design	Randomized Control Trial	Cross-sectional	Cohort	Case-control
Study population	Highly selected population; highly controlled environment	Diverse population observed in a range of settings	Diverse population observed in a range of settings	Diverse population observed in a range of settings
Directionality	Exposure is assigned before outcome is ascertained	Exposure and outcome ascertained simultaneously	Exposure is ascertained before outcome is ascertained	Outcome is ascertained before exposure is ascertained
Primary Use	Demonstrating efficacy of an intervention	Screening hypotheses; prevalence studies	Assessing association between multiple exposures and outcomes over time	Assessing associations between exposures and rare outcomes
Analysis	Straight-forward	Sophisticated multivariate techniques may be required to account for confounding	Sophisticated multivariate techniques may be required to account for confounding	Sophisticated multivariate techniques may be required to account for confounding
Internal validity	High	Low	Low	Low
External validity	Low-Moderate	High	High	High

Carlson M & Morrison RS. Study Design, Precision, and Validity in Observational Studies

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Threats to the Validity of Real World Data (RWD)

- Confounding
- Measurement error
- Selection bias
- Missing data

11

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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

12

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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 $a \geqslant 0$ and 0 otherwise; $\delta(a) = 1$ if $a = 0$ and 0 otherwise

EXAMPLE 2

$$g_\phi(m|u) = \prod_{i=1}^{n_1} \delta(1-m_i) \prod_{i=n_1+1}^{n} \delta(m_i),$$

where n_1 is the minimum k such that the function $Q_k(u_1, \ldots, u_k) \in C$

EXAMPLE 3

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

EXAMPLE 4

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Terminology

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- 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

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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
  - $P(M|Y) = P(M|Y_{miss}, Y_{obs}, \theta) = P(M|\theta)$; $M = 1$ if Y is missing, and 0 otherwise
    - θ indicates conditions of Y_{miss} (e.g., if θ = weight > 120kg 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_{miss}.
  - $P(M|Y) = P(M|Y_{miss}, Y_{obs}, \theta) = P(M|Y_{obs}, \theta)$
- Missing Not at Random (MNAR)
  - Anything else (also known as Nonignorable Nonresponse)
  - Missing values depend on the value of the unobserved result
  - $P(M|Y) \neq P(M|Y_{obs}, \theta)$

17

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

18

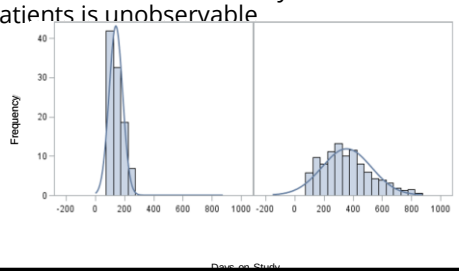
An Example: Informative Censoring

- 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

19

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



20

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

21

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Example: Informative Censoring

- Sensitivity analyses
  - Let θ 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)

22

Example: Informative Censoring

- Sensitivity analyses cont.
  - Exploratory: Condition on changes to the definition of censoring using Rx gaps
    - Let θ 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

Treatment Gap	HR	95% CI	P-value
Time to first gap > 30 days			
Unadjusted hazard ratio (95% CI)	1.21	(1.05,1.39)	**0.0092**
Adjusted hazard ratio (95% CI)	1.40	(1.15,1.71)	**0.0007**
Time to first gap > 60 days			
Unadjusted hazard ratio (95% CI)	1.18	(1.02,1.37)	**0.0230**
Adjusted hazard ratio (95% CI)	1.45	(1.18,1.77)	**0.0003**
Time to first gap > 90 days			
Unadjusted hazard ratio (95% CI)	1.16	(1.00,1.35)	**0.0443**
Adjusted hazard ratio (95% CI)	1.43	(1.16,1.76)	**0.0007**

Example: Informative Censoring

- Sensitivity analyses cont.
  - Other considerations on θ
    - θ based on comorbidities would have been promising, but the EMR was flawed with little information recorded at baseline
    - θ 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 θ such that MAR was considered valid: $\mathrm{P}(M|Y) = P(M|Y_{obs}, \theta)$
  - 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 generalizations

References

- U. S. Food and Drug Administration/Center for Devices and Radiological Health (2017). Guidance for Industry: Use of Real-World Evidence to Support Regulatory Decisions-Making for Medical Devices. (FDA Maryland).
- Sherman, Rachel E., et al. "Real-world evidence - what is it and what can it tell us." *New England Journal of Medicine.* 375.23 (2016): 2293-2297.

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

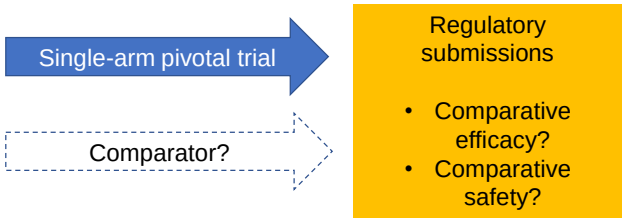
- Case 1: on comparative effectiveness (e.g., in cancer and rare diseases)
- Case 2: on dynamic drug effects on long term outcomes (e.g., Alzheimer´s disease)

- **Case 1: RWD to replace missing data on comparative effectiveness**

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



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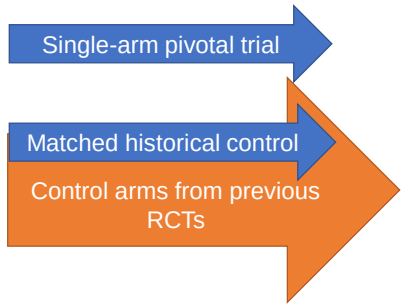
Classical solution: use control arm of previous RCTs as historical control

- *Historical data choice*: to fit the Pocock[1] criteria for suitaiblity (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 disease[2] and Ankylosing Spondylitis[3]
  - Lamotrigine XT in epilepsy[4]
  - 44 indications approved by EMA, 60 by FDA[5] in total between 1999-2014:



[1]*Pocock 1976. J. Chron. Dis. 29:175-178;* [2]*Hueber et al. Gut. 2012 61(12):1693-700;* [3]*Baeten et al. Lancet 2013; 382;1705-13.*
[4]*French et al. Neurotherapeutics 2012. 9:176-184;* [5]Hatswell et al. BMJ open. 2017.

31

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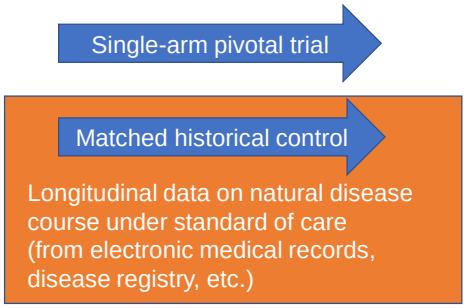
What do to when no RCT exist to use as historical control?

Typical situation for rare and/or very specific cancer indications

→ Leverage RWD to fill missingness in control data and evaluate comparative efficacy



32

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Recent FDA approvals where RWD was used as historical/external control of the pivotal single-arm study

Drug	Indication	Sponsor Year	Type of RWD submitted as historical control	Endpoint for comparative efficacy
Blincyto[1]	Sub-type of acute lymphoblastic leukemia (ALL)	Amgen 2018	Medical records for 121 patients over 8 years from 14 institutions in the US, Canada, Australia - Prospectively planned, retrospective study	CR
Brineura[2]	Batten disease (CLN2)	BioMarin 2017	Disease registry of 69 children (42 included): records & patient interviews - Prospectively planned, mostly retrospective study	CLN2 rating scale (motor, language)
Bavencio[3]	Metastatic Merkel cell carcinoma	EMD Serono 2017	Electronic medical records from 686 patients (14 included) from community and academic centers - Prospectively planned, retrospective study	RECIST
Exondys 51[4]	Duchenne Muscular Distrophy	Sarepta 2016	2 natural disease history cohorts (Belgium & Italy) of about 90 patients each (13 included) - Post-hoc retrospective study	6-min walking test

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

33

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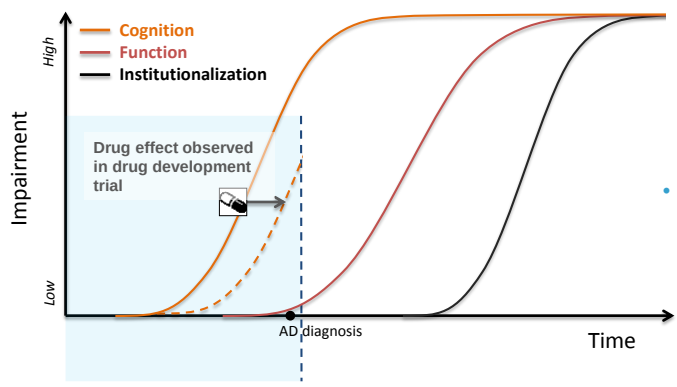
Recent FDA approvals where RWD was used as historical/external control of the pivotal single-arm study

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

34

- **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)

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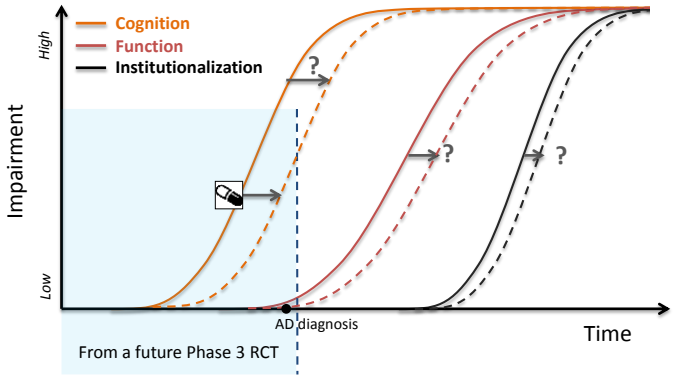
Drug effect on long term Alzheimer´s disease outcomes that are clinically relevant?



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

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

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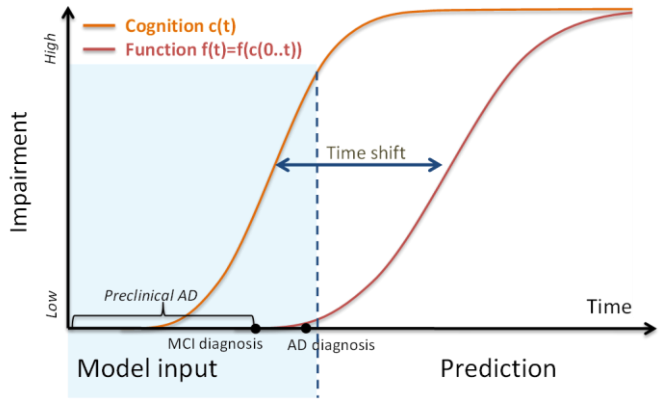
Solution: use several disease registries to develop a series of dynamic models that stitch together outcomes sensitive in different parts of the disease spectrum



Data sources

Disease registries of subjects visiting a memory clinic

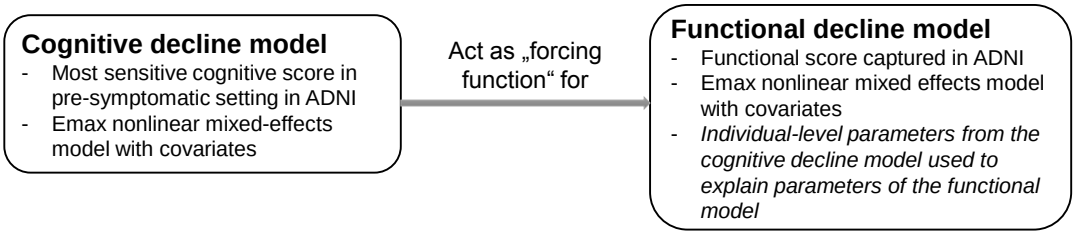
E.g.: ADNI, NACC, Rush, Memento, Goetenburg...

- Solution vetted by a panel of regulatory & HTA experts last February as part of the European Roadmap consortium.

ROADMAP
Real world Outcomes across the AD spectrum for better care

38

An example of such model developed on ADNI data*
Link longitudinal decline in cognition to later decline in function



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

*Karcher, Qi, Hummel, Risson, Capkun-Niggli, Savelieva. Dynamic Alzheimer´s disease model to predict functional decline from a patient´s longitudinal data on cognitive decline. Manuscript in preparation.

39

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

40

Missingness in Real World Studies

Judith Stephenson, SB, SM

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

42

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

43

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

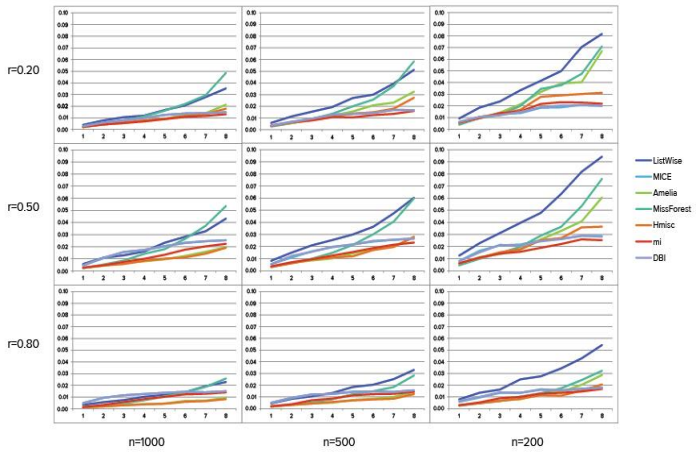
44

Summary of imputation methods

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

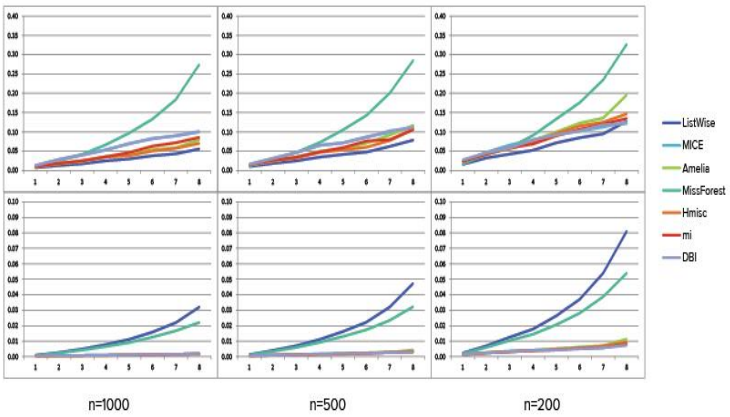
Model R2

- 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

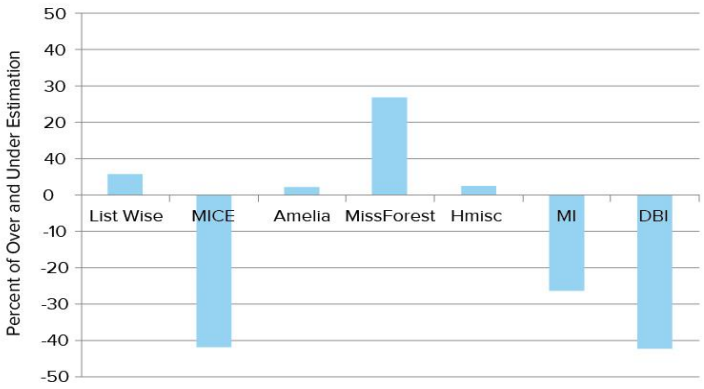
- Smaller the sample size, worse estimates of B and SE-B
- Best estimators of B: LD, mi and Hmisc
- Worst estimators of B: MissForest, MICE and DBI
- Best estimators of SE-B: MICE, Amelia, Hmisc, mi and DBI
- Worst estimators of SE-B: LD and MissForest



47

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 R2: LD, Amelia and Hmisc
- 4 estimators demonstrated high levels of bias for R2: MICE, mi, and DBI underestimated R2 and Mis2sForest overestimated R2



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

49

Missing Data: A Regulatory Perspective

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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 505E (21 U.S.C. 355f) the following:

"SEC. 505F. UTILIZING 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(c); 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.—

"(1) IN GENERAL.—Not later than 2 years after the date of enactment of the 21st Century Cures Act, the Secretary shall establish a draft framework for implementation of the program under this section.

"(2) CONTENTS OF FRAMEWORK.—The framework 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;

TITLE III—DEVELOPMENT

Subtitle A—Patient-Focused Drug Development

Subtitle B—Advancing New Drug Therapies

Subtitle C—Modern Trial Design and Evidence Development

Subtitle D—Patient Access to Therapies and Information

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"(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 tools.
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. Novel 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.

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"(d) 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.

"(e) 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 (a); 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.

"(f) RULE 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 nonspecified 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 evidence standard in such subsection (d); or

TITLE III—DEVELOPMENT

Subtitle A—Patient-Focused Drug Development

Subtitle B—Advancing New Drug Therapies

Subtitle C—Modern Trial Design and Evidence Development

Subtitle D—Patient Access to Therapies and Information

Contains Nonbinding Recommendations

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

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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 that term is defined under section 201(h) 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 and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices. RWD sources (e.g., registries, collections of EHRs, and administrative and healthcare claims databases) can be used as data collection and analysis infrastructure to support many types of trial designs, including, but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies (prospective and/or retrospective).

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.

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

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Under the right conditions, data derived from real world sources can be used to support regulatory decisions. RWD and associated RWE may constitute valid scientific evidence depending on the characteristics of the data. This guidance should not be construed to alter, or change in any way, the existing evidentiary standards applicable to FDA's regulatory decision-making; rather, it describes the circumstances under which RWD may be used to support a variety of FDA decisions based on the existing evidentiary standards. While FDA encourages the use of relevant and reliable RWD, this guidance neither mandates its use nor restricts other means of providing evidence to support regulatory decision-making. This guidance highlights some of the potential uses of RWD, and describes the factors that FDA considers when evaluating whether specific RWD is of sufficient quality to inform or support a regulatory decision. It also clarifies when an Investigational Device Exemption (IDE) may be needed to prospectively collect and use RWD for purposes of determining the safety and effectiveness of a device.

This document does not address the use of non-clinical data, adverse event reports, secondary use of clinical trial data (e.g., post hoc analyses), or systematic literature reviews. Nor does it address study design/conduct or analytical methodologies. While it does describe the factors that FDA considers when evaluating RWD or RWE, it does not provide a specific set of pass/fail criteria or other scoring tools for making a determination about the suitability of RWD or RWE for a particular regulatory decision.

This guidance does not affect any federal, state or local laws or regulations, or foreign laws or regulations that may be applicable to the use or collection of RWD, or that provide protections for human subjects (including informed consent requirements) or patient privacy. This guidance should be used to complement, but not supersede, other device-specific and good clinical practice guidance documents.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

To protect and promote the public health, FDA needs to understand and evaluate the available evidence related to regulated products.[1] For medical devices, available evidence is traditionally comprised of non-clinical and, in some cases, clinical studies conducted and provided to FDA by the device manufacturer or sponsor. However, FDA recognizes that a wealth of RWD covering medical device experience exists and is routinely collected in the course of treatment and management of patients. Data collected during clinical care or in the home setting may not have the same quality controls as data collected within a clinical trial setting. Even so, under certain

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A. Relevance

The relevance of RWD, RWD sources, and resultant analysis is assessed by evaluating several factors as outlined below. These factors can help determine if the data adequately address the applicable regulatory question or requirement, in part or in whole. Questions about the applicability of RWD to a specific case should be discussed with FDA through the pre-submission process.[21] Relevance of RWD for regulatory decision-making can be assessed prior to a regulatory submission, such as via the pre-submission process, or during the regulatory review process. The overall assessment of relevance should determine whether the existing RWD source is adequate for evaluating the performance of a device in the identified regulatory context (as a sole source or partial source of evidence).

Since RWD sources are usually developed for non-regulatory purposes (e.g., to document care in the case of EHRs or to submit insurance claims for reimbursement in administrative and claims data), FDA will assess whether the individual data elements contained within an existing RWD source are sufficient to be used for a regulatory purpose. The data should be accurate, as complete as possible, and have an appropriate scope to address the question at hand (i.e., data adequacy). The need for review or adjudication of specific outcomes of interest (e.g. stroke or major bleeding) at the patient level may also be assessed. For analysis and interpretation of RWD, it is important to have a pre-defined common set of data elements, a common definitional framework (i.e., data dictionary), and pre-specified time intervals for data element collection and outcome analyses. In assessing the relevance of RWD, FDA will also consider, if warranted, the ability to supplement the available RWD through linkage with other data sources to provide additional or confirmatory data, e.g., with EHR and/or administrative claims data.

Important relevance factors that FDA will assess to determine if the RWD are suitable for regulatory use include, but are not limited to, whether:

- the RWD contain sufficient detail to capture the use of the device, exposures, and the outcomes of interest in the appropriate population (i.e. the data apply to the question at hand);
- the data elements available for analysis are capable of addressing the specified question when valid and appropriate analytical methods are applied (i.e. the data are amenable to sound clinical and statistical analysis); and
- the RWD and RWE they provide are interpretable using informed clinical/scientific judgment. Important considerations for the assessment of this factor include:

[21] Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff: Guidance for Industry and Food and Drug Administration Staff (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf)

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- whether the use of the device in a real-world population is representative as captured within the data source, and is generalizable to the relevant population being evaluated;
- whether the RWD source is used regionally, nationally and/or internationally;
- the overall percentage of patient exposure to the device that are captured in the RWD source;
- the validation protocols and resultant data that are used to evaluate how well the RWD source reflects the patient population's experience;
- whether the RWD study design, study protocol, and/or analysis plan is appropriate to address the regulatory question and capable of being accomplished in a sufficiently timely manner;
- whether the RWD contains elements to capture specific device identification information (e.g., unique device identifier);
- whether the RWD adequately captures patient medical history and preexisting conditions, as well as follow-up information needed evaluate the question being addressed (e.g., whether administrative claims data have adequate continuity of coverage);
- whether sufficient data elements are collected to adjust for confounding factors that may impact the exposure or outcomes of interest;
- whether any linkages performed are scientifically appropriate and account for differences in coding and reporting across sources;
- the RWD source reporting schedule, including time interval between database close and release, and length of reporting periods;
- the prior documented (e.g., peer reviewed publications or practice guidelines) use of the RWD source for determining outcomes-based quality assessments, validated predictive risk modeling, signal detection, performance improvement, benchmarking, and other clinically-meaningful uses;
- whether the data elements collected are sufficient for assessing outcomes (including adjudication, if necessary); and
- whether supplemental data sources are available and sufficient to provide any missing information or evidence required for an informed decision.

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- whether necessary and adequate patient protections were in place (e.g., methods to protect patient privacy, and need for informed consent as determined by the reviewing IRB and in compliance with FDA regulations).

(2) Data assurance - Quality Control

Data quality control is essential for providing confidence in the reliability of RWD and RWE sources. RWD quality can generally be improved by following published recommendations concerning registries, such as those by the Agency for Health Care Quality, Patient-Centered Outcomes Research Institute,[22] the National Medical Device Registry Task Force,[23] and the Regulators Forum (IMDRF) Registry Working Group. [24] However, certain sources of RWD, such as some administrative and healthcare claims databases or EHRs, may not have established data quality control processes and may not be capable of fully implementing or following the above recommendations. When considering a source of RWD for regulatory purposes, it is important to consider any methods and systems used to help ensure sufficient data quality. Potential RWD sources should be evaluated in accordance with the data QA plan and procedures developed for the data source itself. Since evaluation of RWD sources may not always permit specific line item source verification, important factors for consideration include:

- the quality of data element population (e.g., whether abstracted from a verifiable source to assess transcription errors or automatically populated through a data extraction algorithm);
- adherence to source verification procedures and data collection and recording procedures for completeness and consistency;
- completeness (i.e., minimized missing or out of range values) of data necessary for specified analyses, including adjustment for confounding factors;
- data consistency across sites and over time; [25]

[22] AHRQ Registries for Evaluating Patient Outcomes: A User's Guide 3rd Edition, Volume 1 Chapter 11, Data Collection and Quality Assurance and Volume 2 Chapter 25, Assessing Quality. (http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&mp=1&productID=1897)
[23] A Report from the Medical Device Registry Task Force & the Medical Devices Epidemiology Network. Recommendations for a National Medical Device Evaluation System. Strategically Coordinated Registry Networks to Bridge Clinical Care and Research, August 2015. Available at: http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm459368.pdf. Accessed August 6, 2016.
[24] IMDRF Registry Essential Principles. Available at: http://www.imdrf.org/docs/imdrf/final/consultations/imdrf-cons-essential-principles-151124.pdf. Accessed August 3, 2016
[25] PCORI Conduct of Registry Studies http://www.pcori.org/sites/default/files/Standards-in-the-Conduct-of-Registry-Studies-for-Patient-Centered-Outcomes-Research1.pdf

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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 increased dropout rate), consider a randomized withdrawal design, in which only participants who have already received a study treatment without dropping out undergo 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

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Methods for Handling Missing Data

Statistical method for handling missing data†	
Method not stated	14 (16%)
Complete-case analysis assumed	9 (11%)
Complete-case analysis	54 (66%)
Weighted	1
Unweighted	53
Exclude participants with missing data at any repeated waves of exposure	38
Exclude participant data record for waves of data collection with missing exposure data††	15
Missing Indicator Method	1 (1%)
Mean value substitution	3 (4%)
Last Observation Carried Forward	7 (9%)
Multiple Imputation	5 (6%)
Details provided for the multiple imputation:	
Indicated how many imputations were performed	4
Indicated which variables were included in the imputation model	2
Compared results from multiple imputation with complete case analysis	3
Performed a sensitivity analysis under different assumptions for missing data	4
Fully Bayesian Model	1 (1%)

Karahalios A et al. A review of the reporting and handling of missing data in cohort studies with repeated assessment of exposure measures

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- 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.

DEVELOPMENT

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The Prevention and Treatment of Missing Data in Clinical Trials: An FDA Perspective on the Importance of Dealing With It

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At the request of the Food and Drug Administration (FDA) and with its funding, the Panel on the Handling of Missing Data in Clinical Trials was created by the National Research Council's Committee on National Statistics. This panel recently published a report[1] with recommendations that will be of use not only to the FDA but also to the entire clinical trial community so that the latter can take measures to improve the conduct and analysis of clinical trials.

One of the FDA's reasons for seeking such a report was to develop recommendations that would contribute to a guidance for dealing with missing data in clinical trials and, wherever possible, for decreasing the extent of such missing data. A guidance would be directed toward the pharmaceutical industry, but we hope that it will be useful to the broader clinical trial community. The goal of such a guidance would be twofold: first, to prevent missing data, insofar as that is possible, through changes in study design and subject follow-up methods, and second, to use appropriate statistical methods to deal with missing data in clinical trials.

This article is intended to share with a larger audience the importance of addressing the missing data problem in clinical trials, particularly the steps that may be taken to reduce the extent of missing data. The regulatory drug and biologics review process in the United States helps to ensure the quality of the clinical trials that will be submitted in support of marketing, and it provides a regulatory-science base to advance new methods, approaches, and innovations. Indeed, this is a large part of the FDA's mission.[2]

BACKGROUND

The randomized clinical trial, long the primary method of drug testing, relies on random assignment to treatments to remove potential bias in the estimation of treatment effects. The FDA's regulations on adequate and well-controlled trials and substantial evidence clearly articulate this point. Inherent in this principle, but not fully recognized until recent years, is the importance of being reasonably sure that when patients leave a study before the protocol-specified completion time (resulting in missing outcome data with respect to these patients beyond their respective withdrawal dates), the benefits of randomization have not been compromised—which could be the case if the withdrawals were treatment related and therefore not random. A classic remedy, at least in outcome studies, is to attempt to measure outcomes in all the subjects who were initially randomized, including those who withdraw from therapy; this is the "intent to treat" (ITT) approach to the analysis of clinical trial data. As an example of why this might be important, consider an outcome study (with an end point of survival) in which the test drug exacerbated heart failure. In these circumstances, subjects with heart failure, who might be at an increased risk for death, would be more likely to leave the test-drug group. This would lower the mortality risk in the test-drug group and give that drug an advantage with respect to its safety profile, unless the dropouts were followed and the post-dropout events counted. The ITT approach is intended to protect against this kind of "informative censoring" by requiring that dropouts be followed up and that post-dropout events be counted. It is recognized that an ITT analysis is conservative (after all, the benefits of a drug usually disappear once it is stopped), but this is generally considered acceptable in outcome studies. There are compromise approaches—e.g., counting events that occur within 30 days of stopping treatment, assuming that subjects are followed for that duration and it is possible to ascertain outcomes.

Trials of symptomatic benefit generally measure the effects of assigned treatment at successive visits over the duration of the trial, but they typically use the value measured at the final visit as the primary end point. In such trials, the missing-data problem is of a different kind. Early dropouts can leave treatment groups unbalanced with respect to important prognostic patient

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550

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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/m^2 or greater (obese) (1) or
  - 27 kg/m^2 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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