Recruitment Strategy for Prospective Observational Studies to Mimic Randomization

Up-Front Matching

Ibrahim Turkoz, PhD
Janssen R&D, LLC
04 Nov 2024

Based on manuscript: Up-front matching: an ongoing recruitment method for prospective observational studies that mimics randomization for selected baseline covariates. ***Journal of Biopharmaceutical Statistics***, 1–14. https://doi.org/10.1080/10543406.2024.2373436

Johnson&Johnson
Innovative Medicine

Agenda

Regulatory Environment for using RWD/RWE

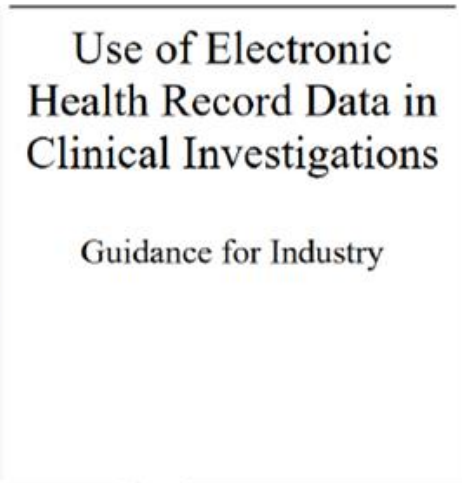
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

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

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.



Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

U.S. FOOD & DRUG ADMINISTRATION

FRAMEWORK FOR FDA'S

REAL-WORLD EVIDENCE PROGRAM

Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

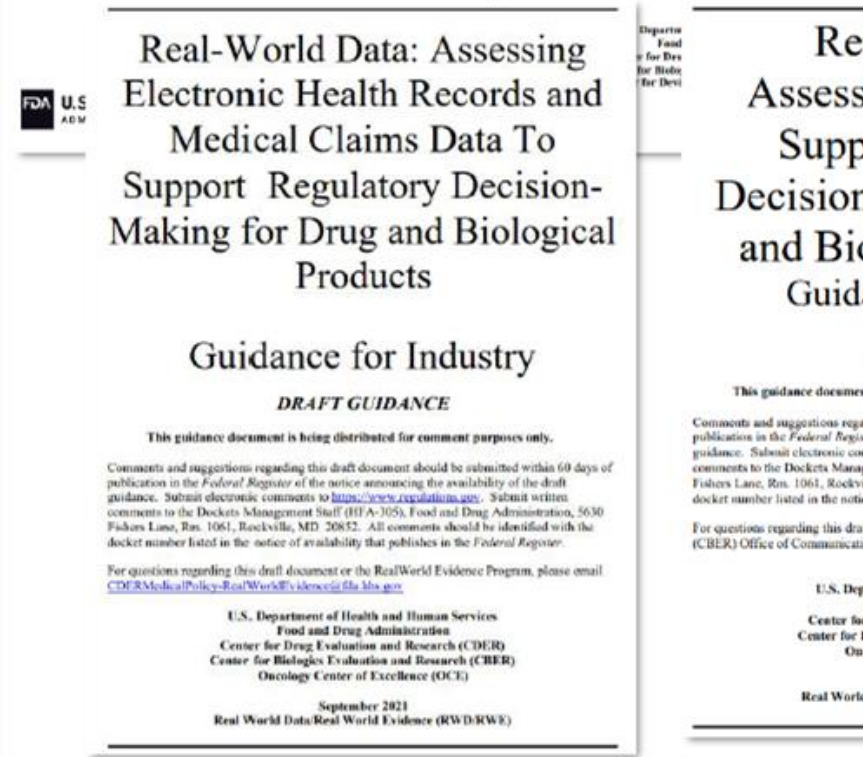
For questions regarding this draft document or the Real-World Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov.

HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY SCIENCE · MEDICINES · HEALTH

European medicines agencies network strategy to 2025

Protecting public health at a time of rapid change



Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

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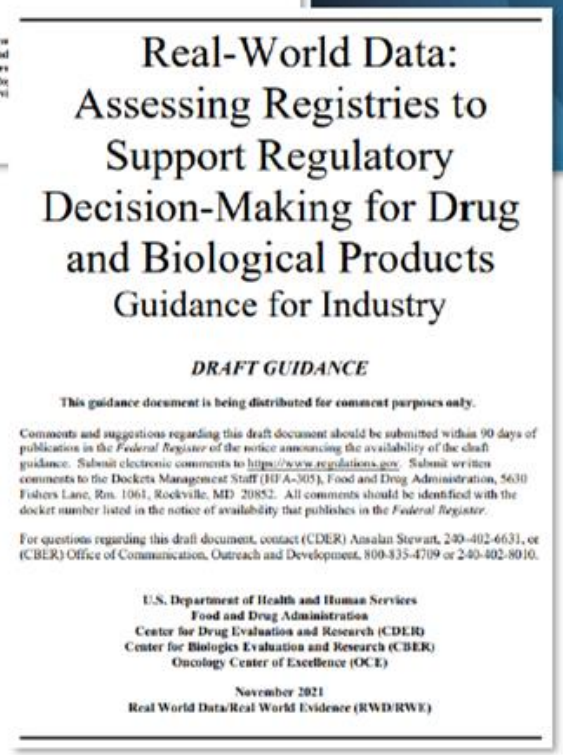
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2021
Real World Data/Real World Evidence (RWD/RWE)



Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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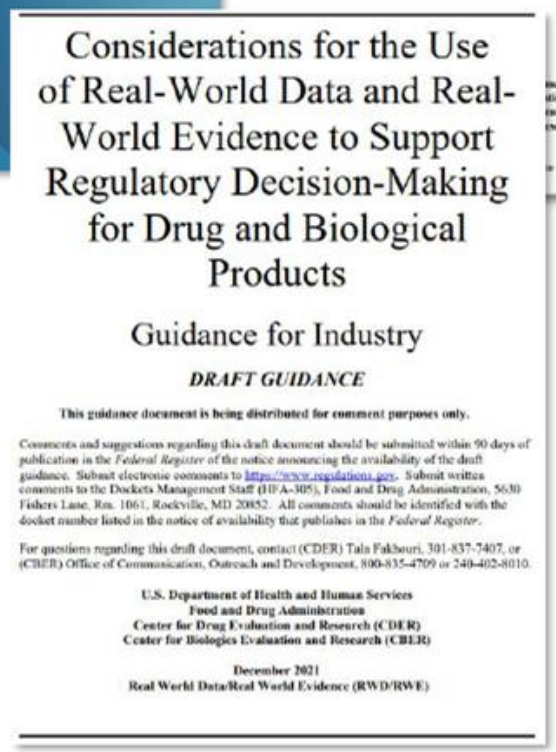
For questions regarding this draft document, contact (CDER) Ansalan Stewart, 240-402-6631, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

November 2021
Real World Data/Real World Evidence (RWD/RWE)



Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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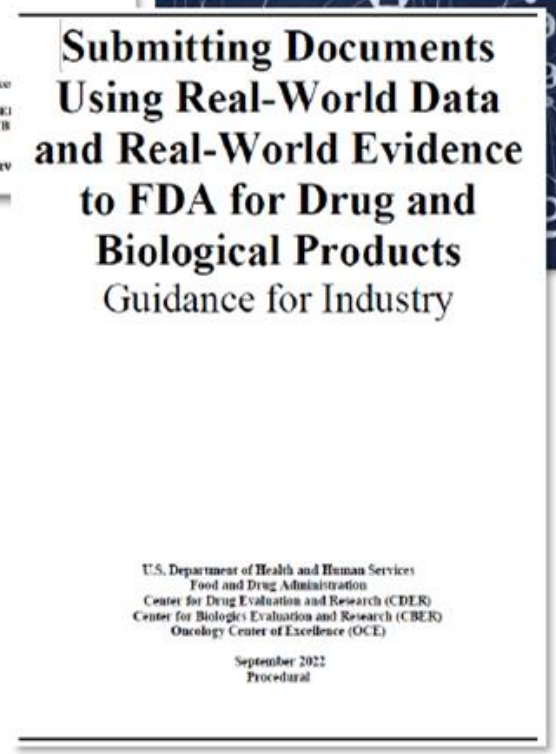
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2021
Real World Data/Real World Evidence (RWD/RWE)



Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2022
Procedural

Key Concepts and Descriptors

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2023
Real-World Data/Real-World Evidence (RWD/RWE)

Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

March 2024
Real World Data/Real World Evidence (RWD/RWE)

55680653dft

Key Concepts and Descriptors

Contemporary Terms for Study Design

- *Interventional studies* (*clinical trials*) – study in which patients are assigned to one or more treatment groups, according to a study protocol, to evaluate the effects of a treatment of interest on subsequent health-related outcomes
  - e.g., *randomized controlled trials*, *single-arm trials*
- *Non-interventional* (*observational) studies* – study in which patients are not assigned to a study arm according to a research protocol, but instead receive the drug of interest during routine medical practice
  - e.g., *observational cohort studies* (patients identified based on drugs received, with subsequent outcomes identified), or *case-control studies* (patients identified based on health outcomes, with antecedent drug use determined)
- *Other study designs*
  - e.g., *externally controlled trials* (single-arm trial & other data source, e.g., RWD source or arm from previously completed trial; includes natural history studies)

Key Concepts and Descriptors:

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

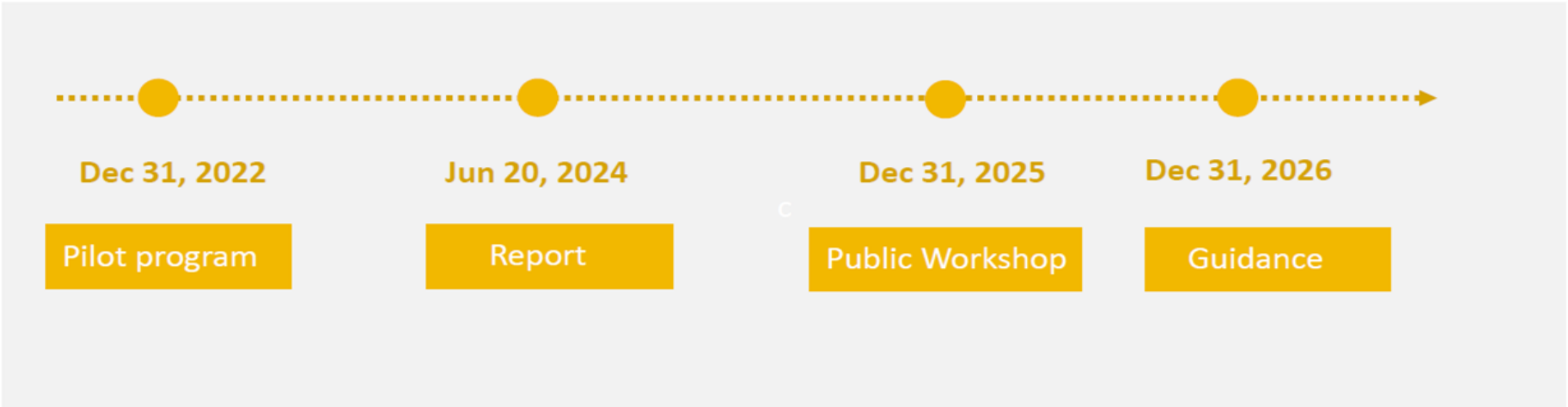
- **electronic health records (EHRs)**
- **medical claims data**
- **product and disease registries**
- **data from digital health technologies in non-research setting**
- **other data sources that can inform on health status, such as questionnaires**

Real-World Evidence (RWE) is clinical evidence regarding the usage and potential benefits/risks of a medical product **derived from analysis of RWD**

Generated using various study designs—including but not limited to **randomized trials (e.g., pragmatic clinical trials)**, externally controlled trials, and observational studies

PDUFA VII: Fiscal Years 2023 – 2027 Commitment Letter

Section 6: Advancing RWE for Use in Regulatory Decision-Making



Source: https://www.fda.gov/media/151712/download

21st Century Cures 2.0 Discussion Draft

TITLE III: FOOD AND DRUG ADMINISTRATION

Sec. 301. Report on Collaboration and Alignment in Regulating Digital Health Technologies: requires the HHS Secretary to submit a report to Congress on the efforts to ensure collaboration and alignment across the centers and offices of the Food and Drug Administration with respect to the regulation of digital health technologies

Sec. 302. Grants for Novel Trial Designs and Other Innovations in Drug Development: provides grants in the area of innovative clinical trial design and patient experience data to further build the science in these areas.

Sec. 303. FDA Cell and Gene Therapy: requires the HHS Secretary to submit a report to Congress re: the current state of cell and gene therapy regulation and foreseeable regulatory challenges for the FDA in the future.

Sec. 304. Increasing Use of Real-World Evidence: builds on FDA's efforts by

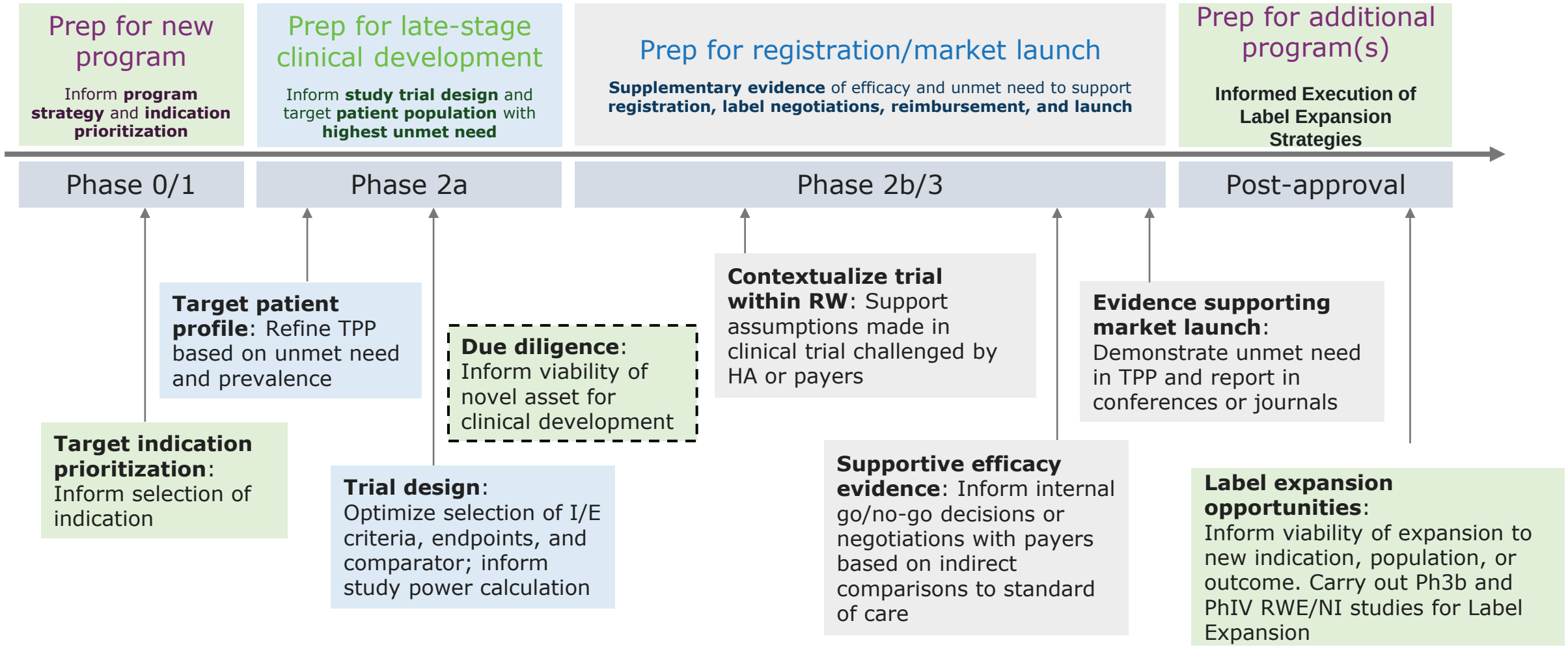
- requiring HHS to outline approaches to maximize and expand the use of RWE; and
- establishing a task force to develop recommendations on ways to encourage patients to engage in real-world data generation.

⋮

Sec. 309. Post-Approval Study Requirements for Accelerated Approval: Allows for use of other evidence, such as clinical evidence, patient registries, or other real-world evidence, to fulfill post-approval study requirements to confirm the predicted clinical benefit of a therapy.

Source: https://degette.house.gov/sites/degette.house.gov/files/Cures%202.0_DD%20SxS_FINAL1.pdf

Partnership throughout the life-cycle



Determining Fit for purpose RWD

Data relevance

- Representativeness of data to target population
- Contains necessary variables and information within variables (**endpoints**)
- Sufficiency of size

Data reliability

- Ascertainment and processing of key variables (unstructured vs. structured)
- Accuracy and consistency (measurement error?)
- Completeness and missing information (linkages to other databases?)

Regulatory issues

- Transparency, traceability, auditability (ownership? Privacy?)
- Data standards and formatting (reproducibility?)
- Data submission

Prospective Observational Studies

Prospective Observational Studies can be one of the best options when a RCTs are not possible to execute.

Strength of Prospective Observational Studies include:

1. Can provide better quality of data on the primary exposure and on confounding variables.
   a. Clear specification of target patient population(s), treatments, and outcomes of interest for making inferences regarding causal effects.
   b. Generate apriori study protocol, build data collection algorithms, state the purpose or main hypotheses, identifies confounders (whether measured or not), specifies the primary analyses and required sample size.
   c. Implement time and even schedules, clinical scales, patient reported outcomes.
   d. Control quality of data.
2. Since exposures are assessed before outcomes occur, they are less prone to bias.
   a. Collect baseline data on all subjects, before any of them have developed the outcomes of interest.

Disadvantages to Prospective Observational Studies include:

1. They could be more expensive and time consuming
2. They are not efficient for diseases with long latency.
3. Must account for measured and unmeasured confounders. Losses to follow up can bias the measure of association.

Challenges Associated with the Use of RWE/Observational Studies

- Selection Bias
- Information Bias

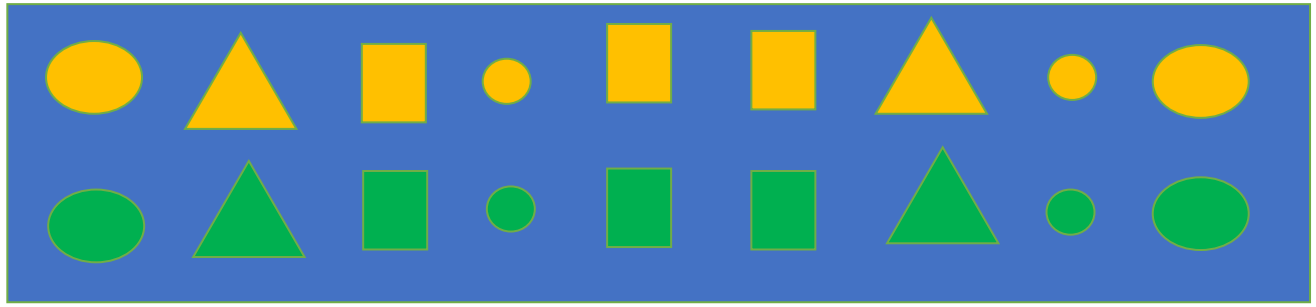
  -memory bias

  -interviewer bias
- Confounding

Randomized Clinical Trial vs. Observational Study

Green: patients who receive treatment A
Yellow: patients who receive treatment B

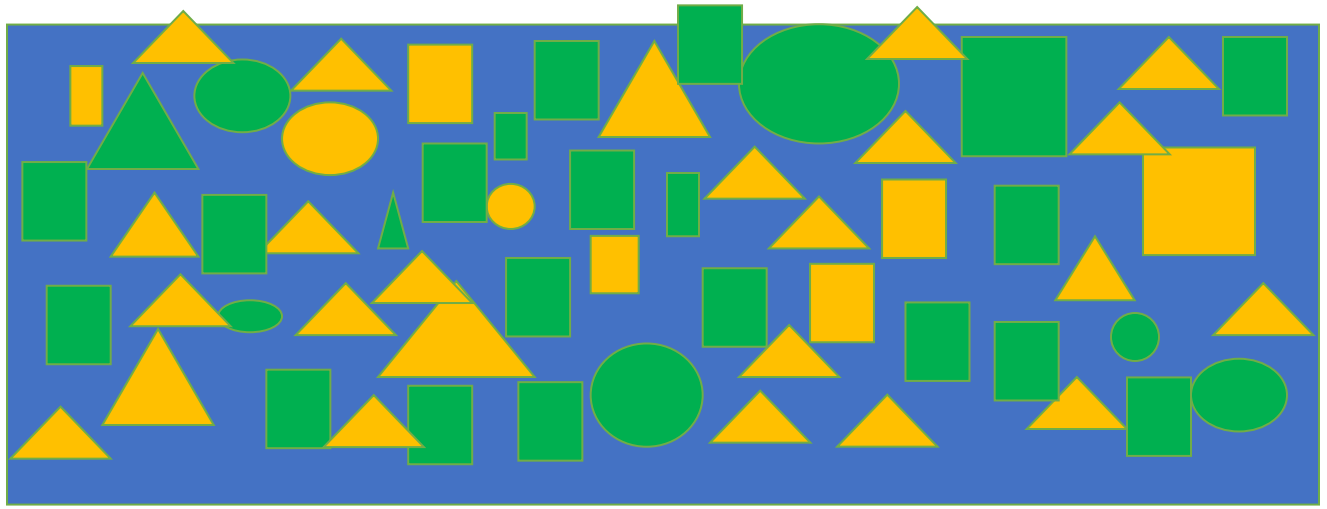
Randomized Clinical Trials



- With randomization – standard methods produce estimates of causal treatment effects

Randomized Clinical Trial vs. Observational Study (continued)

Observational Study

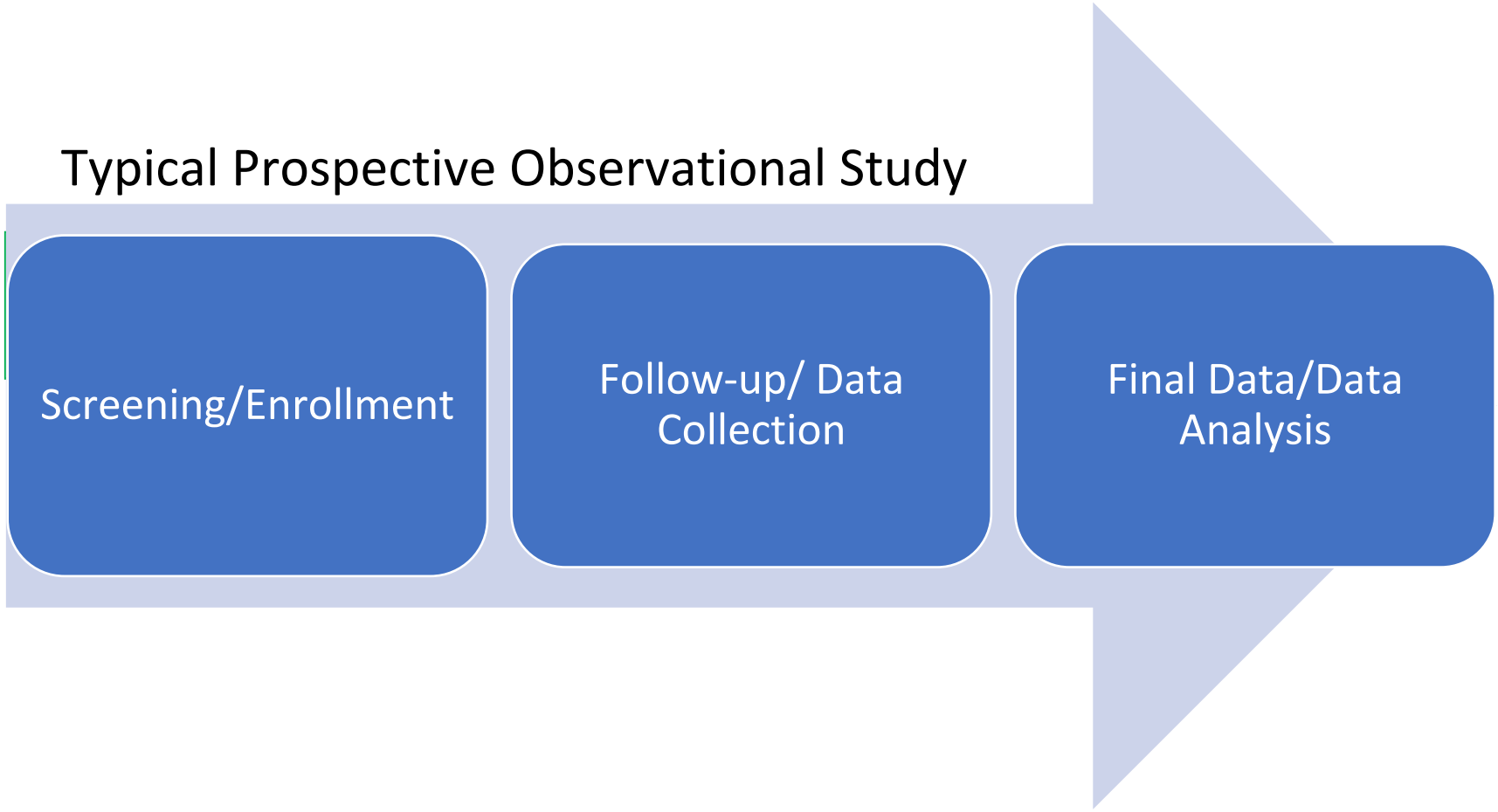


- <u>Without randomization</u> – standard methods produce only ‘associations’ …. Treatment groups are NOT comparable prior to drug/intervention initiation, thus comparisons are BIASED

Matching and Weighting (Pro's and Con's)

	Pro's	Con's
Matching	Very straightforward, easy to communicate with clinicians	May discard some unmatched observations Matched sample might no longer represent target population. Less efficient, lost in power Some methods predetermine your target estimator and: Your estimand is ATT with 1:1 & 1:m matching. Extension to longitudinal setting is limited.
Weighting	Often utilize larger set of observations; more efficient, higher power Can extend to longitudinal setting : use MSM to control for time varying confounding	Large weights can be problematic : distort your target population depending on how you deal with the large weights Some may misunderstand the method

Typical Prospective Observational Study



Typical Prospective Observational Study

Screening/Enrollment

Follow-up/ Data Collection

Final Data/Data Analysis

TRT A

TRT B

Typical Prospective Observational Study

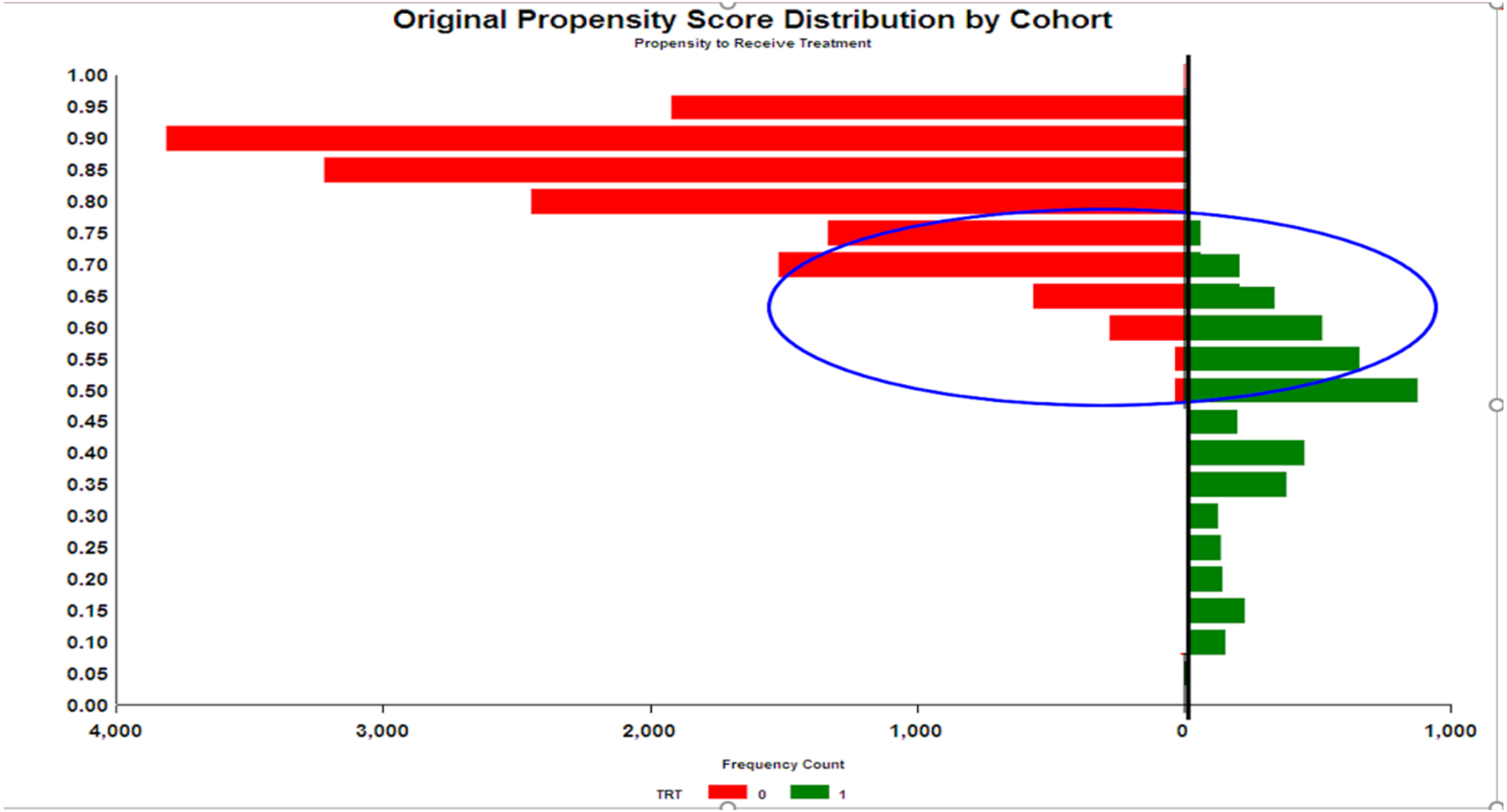
Screening/Enrollment

Follow-up/ Data Collection

Final Data/Data Analysis

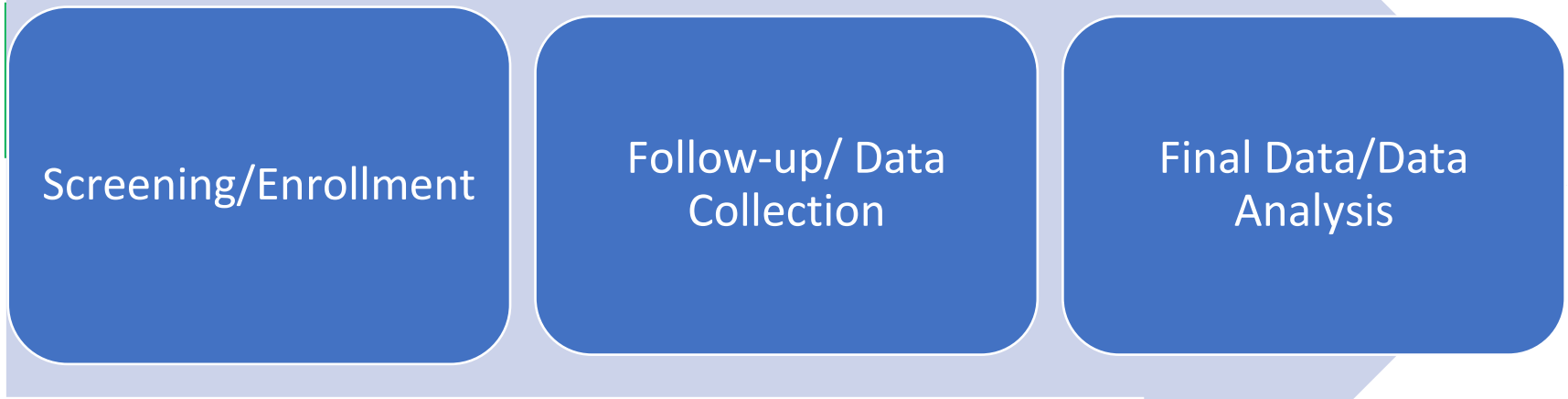
TRT A

TRT B


Original Propensity Score Distribution by Cohort
Propensity to Receive Treatment
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
4,000
3,000
2,000
1,000
0
1,000
Frequency Count
TRT
0
1

Up-Front Matching

Typical Prospective Observational Study



TRT A

TRT B

Up-Front Matching Methodology for Selected Covariates

- Objective is to assess the comparative effectiveness of two drugs, say Drug A and Drug B where the patient populations are noticeably different but there is considerable overlap.

- To keep the description relatively concrete suppose we want to assess the average treatment effect in a patient population with characteristics of patients being treated with Drug A, i.e., the average treatment effect in the treated (in this case those treated with Drug A).

Up-Front Matching Methodology for Selected Covariates

- The key to up-front matching is to use of **readily available/accessible (inexpensive) covariates.**

- The goal of up-front matching is to create enrolled populations in the prospective observational study with (1) a higher percentage of patients **in the common support** as determined by the propensity score based on all baseline covariates in the enrolled populations at the end of the study; and (2) **balance across the inexpensive covariates** in the final enrolled populations. Note that the propensity score is used here for its balancing properties (Rosenbaum and Rubin 1983) and not as means to create treatment ignorability as the basis for causal inference; study outcomes play no role in the up-front matching method.

Up-Front Matching Methodology for Selected Covariates

Up-front matching is performed as follows:

a-) Determine the common support based on the propensity score ($\pi(s)$) distributions of the two treatment groups in the claims database.
b-) Determine the deciles of the propensity score distribution of Drug A; we are interested in enrolling patients in both groups who have pretreatment characteristics like those who were treated with Drug A.
c-) As patients are considered for enrollment, enroll only those whose propensity score is in the common support.
d-) Specify a quota of patients to be enrolled for each treatment group in each decile. For our illustration we take this quota to be the same for each treatment-decile combination – this is stratified matching (on the propensity score), a form of statistical sampling that is alternatively known as frequency matching.
e-) For each treatment group once the quota in a treatment-decile group has been filled that treatment-decile is closed to further enrollment.
f-) For each treatment group continue enrolling patients until all treatment-decile quotas for that treatment group have been met.

Simulation Set-up

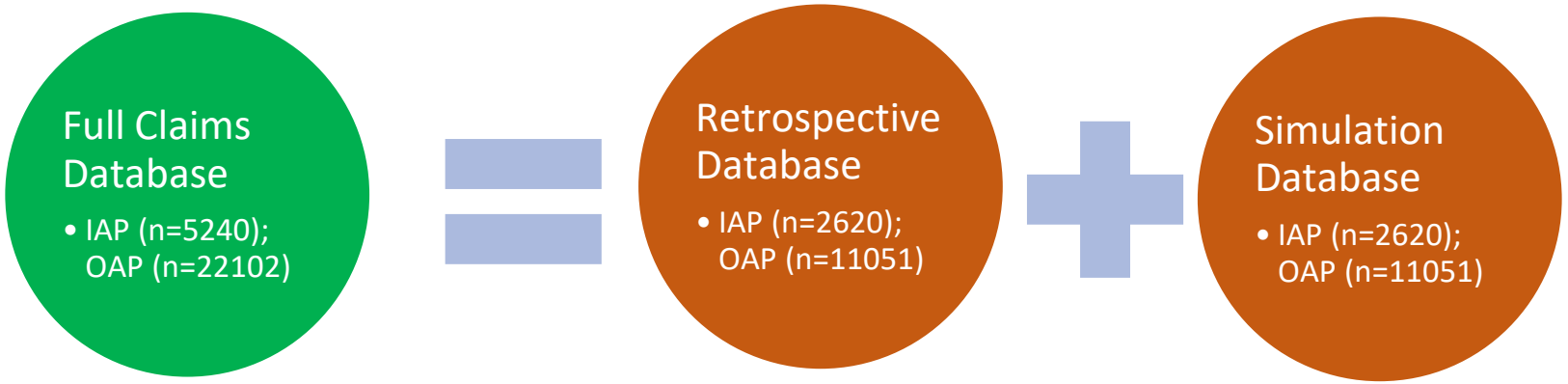
Table 1 - Summary of Propensity Score Covariates in Claims Database – Full Patient Population

Variables	IAP (n=5240)		OAP (n=22102)		Standardized Difference in Means[1]
	Mean	Variance	Mean	Variance	
Number of anti-psychotics prescribed (*n.antipsychotics*)	1.74	1.69	1.18	1.40	0.457
Age at index date, years (*age*)	37.79	171.19	38.19	193.71	-0.030
Number of psychiatric hospitalizations (*num.psych.hosp*)	0.78	1.91	0.53	1.35	0.200
Number of psychiatric drugs prescribed (*n.all.psychiatric.drugs*)	3.97	8.64	3.66	8.57	0.108
Gender (*male*)	0.41	0.24	0.51	0.25	-0.194
Race (*white*)	0.36	0.23	0.43	0.24	-0.138
Race (*black*)	0.48	0.25	0.41	0.24	0.145
Race (*Hispanic*)	0.02	0.02	0.02	0.01	0.003
Race (*other*)	0.15	0.12	0.15	0.13	-0.013

IAP: injectable atypical anti-psychotics; OAP: oral atypical anti-psychotics. Variable names are listed within the parentheses.

(1) The difference in the means (IAP minus OAP) divided by the square root of the average of the variance in the 2 groups.

Simulation Set-up



Two recruitment schemes were simulated:

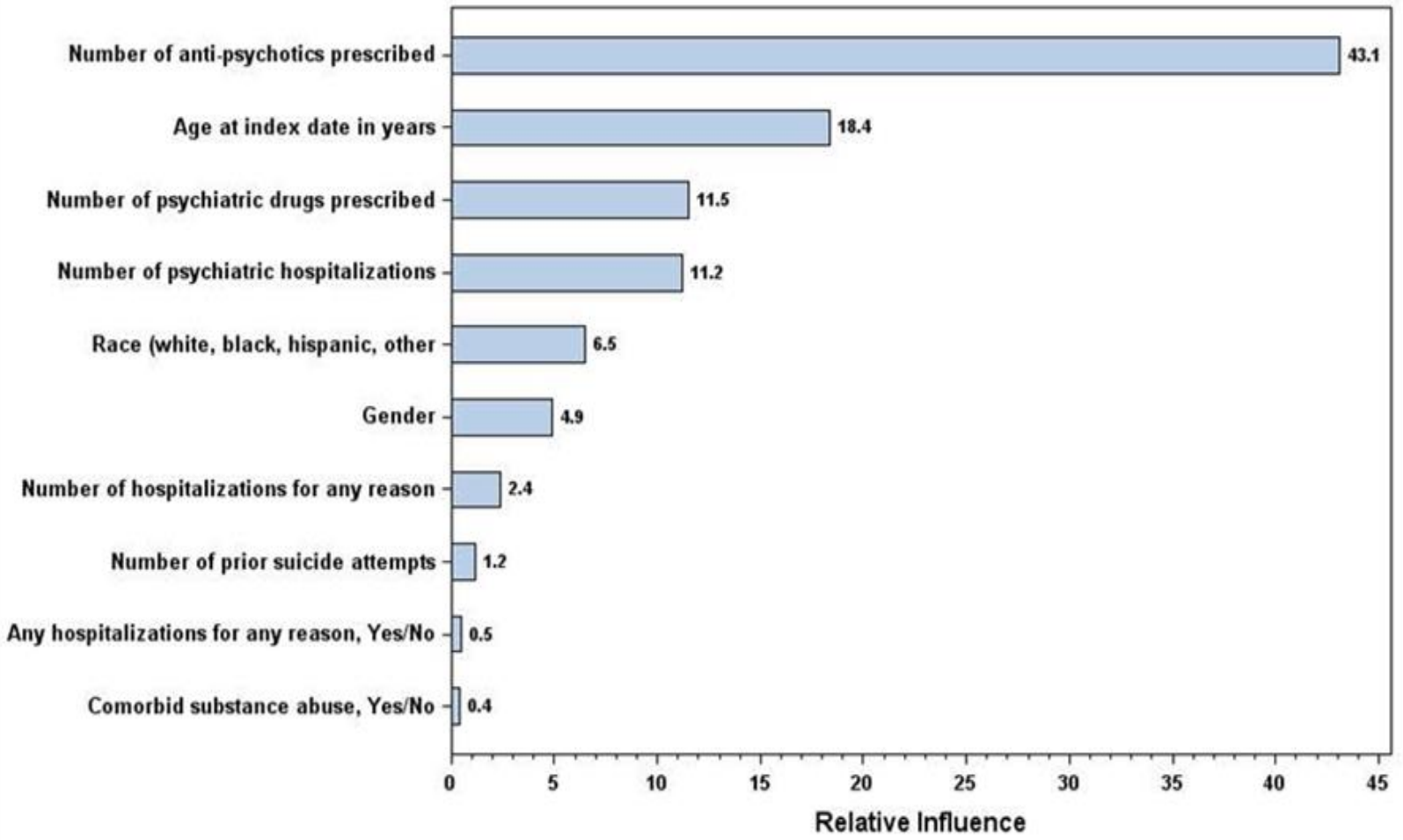
(1) Up-front matching: enrolls patients according to the up-front matching enrollment scheme which is based on the retrospective database

(2) Simple random sampling from the treatment and comparator populations in the simulation database.

*Both schemes consider patients for enrollment that are randomly sampled from the simulation database.

Simulation Results

Matching Variables and Their Relative Influence



Note: All non-demographic variables are based on the 1-year follow-back period

The baseline characteristics deemed to be of interest and ascertainable in both the claims database and in patients who are to be considered for enrollment at investigative sites are given in the Figure along with their relative importance's based on the preliminary propensity score model.

Simulation Results

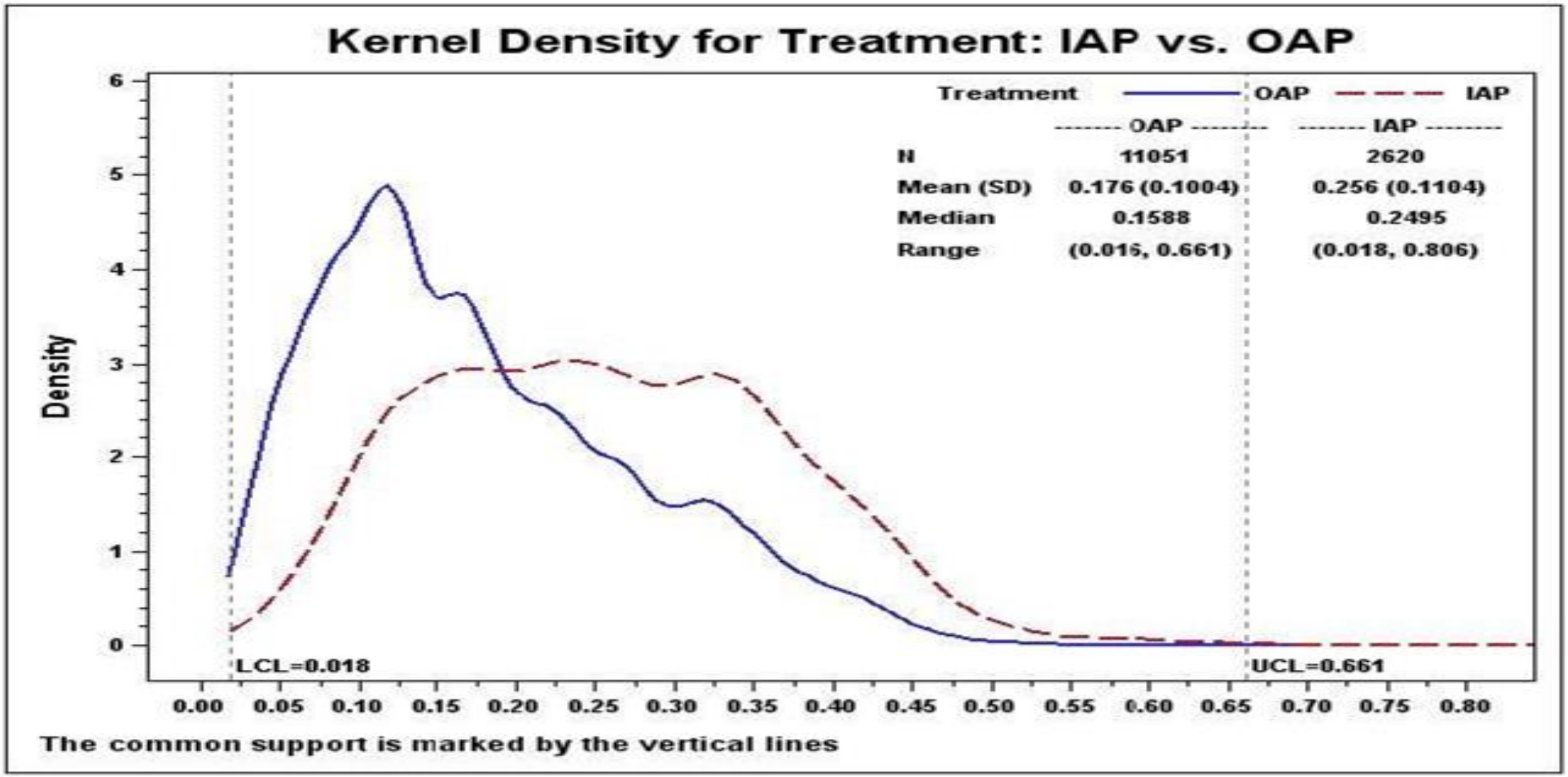
Table 1.a - Summary of Propensity Score Covariates in Claims Database – Retrospective Database

Variables	IAP (n=2620) Mean	IAP (n=2620) Variance	OAP (n=11051) Mean	OAP (n=11051) Variance	Standardized Difference in Means*
Number of anti-psychotics prescribed	1.71	1.84	1.12	1.39	0.464
Age at index date, years	37.61	168.57	37.81	192.57	-0.015
Number of psychiatric hospitalizations	0.85	2.29	0.50	1.31	0.264
Number of psychiatric drugs prescribed	3.95	9.34	3.57	8.66	0.126

IAP: injectable atypical anti-psychotics; OAP: oral atypical anti-psychotics.
*: The difference in the means (IAP minus OAP) divided by the square root of the average of the variance in the 2 groups.

Simulation Results

Distribution of Propensity Scores for IAP and OAP groups

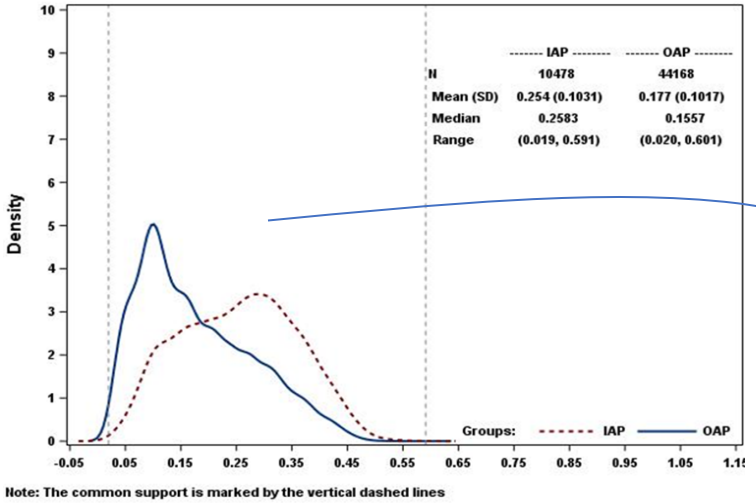


Simulation Results

Table 1.b - Summary of Propensity Score Covariates in Claims Database - Simulation Database

Variables	IAP (n=2620) Mean	IAP (n=2620) Variance	OAP (n=11051) Mean	OAP (n=11051) Variance	Standardized Difference in Means*
Number of anti-psychotics prescribed	1.78	1.54	1.23	1.41	0.451
Age at index date, years	37.97	173.77	38.57	194.58	-0.044
Number of psychiatric hospitalizations	0.72	1.52	0.56	1.39	0.129
Number of psychiatric drugs prescribed	4.00	7.95	3.74	8.45	0.089

IAP: injectable atypical anti-psychotics; OAP: oral atypical anti-psychotics.
*: The difference in the means (IAP minus OAP) divided by the square root of the average of the variance in the 2 groups.

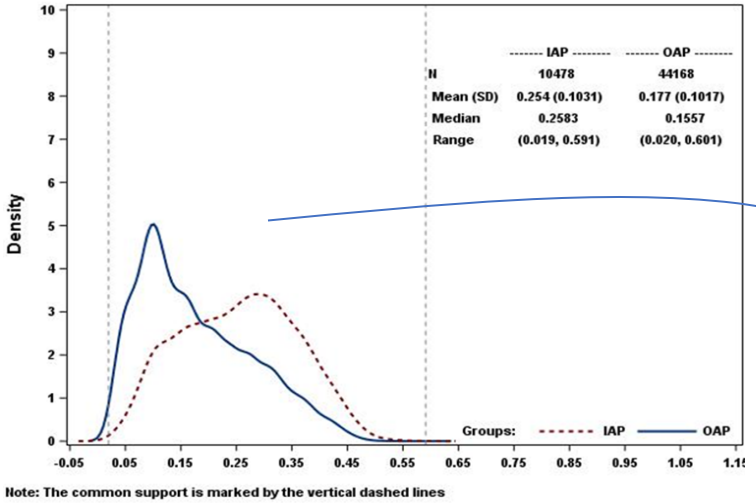


Stratum 1, n=20
Stratum 2, n=20
Stratum 3, n=20
Stratum 4, n=20
Stratum 5, n=20
Stratum 6, n=20
Stratum 7, n=20
Stratum 8, n=20
Stratum 9, n=20
Stratum 10, n=20

IAP, n=200

Stratum 1, n=20
Stratum 2, n=20
Stratum 3, n=20
Stratum 4, n=20
Stratum 5, n=20
Stratum 6, n=20
Stratum 7, n=20
Stratum 8, n=20
Stratum 9, n=20
Stratum 10, n=20

OAP, n=200



Stratum 1, n=20
Stratum 2, n=20
Stratum 3, n=20
Stratum 4, n=20
Stratum 5, n=20
Stratum 6, n=20
Stratum 7, n=20
Stratum 8, n=20
Stratum 9, n=20
Stratum 10, n=20

IAP, n=200

Stratum 1, n=20
Stratum 2, n=20
Stratum 3, n=20
Stratum 4, n=20
Stratum 5, n=20
Stratum 6, n=20
Stratum 7, n=20
Stratum 8, n=20
Stratum 9, n=20
Stratum 10, n=20

OAP, n=200

IAP, Π(s)

IAP, Π(s)

Simulation Results

Table 2. Mean and Standard Deviation of SMD_{200}* Under No Up-Front Matching and Up-Front Matching

	No Up-Front Matching		Up-Front Matching	
Variables	Mean SMD_{200}	Standard Deviation of SMD_{200}	Mean SMD_{200}	Standard Deviation of SMD200
Number of anti-psychotics prescribed	0.446	0.103	0.042	0.079
Age at index date, years	-0.045	0.099	-0.015	0.097
Number of psychiatric hospitalizations	0.133	0.108	-0.082	0.093
Number of psychiatric drugs prescribed	0.085	0.101	-0.000	0.094

*: Standardized mean difference based on samples of size 200 across 500 studies.

Simulation Results

Derivations of the Normal Asymptotic Approximation of the Distribution of the Standardized Mean Difference

The sample standardized mean difference is defined by

$$SMD_n \equiv \frac{\overline{X_1} - \overline{X_2}}{\sqrt{\frac{1}{2}\left(s_1^2 + s_2^2\right)}} = \frac{\overline{Z}}{s} .$$

Let

$$T_n \equiv \frac{\sqrt{n}\,\overline{Z}}{s} = \frac{\sqrt{n}\,\overline{Z} \Big/ \sqrt{2}\sigma}{s \Big/ \sqrt{2}\sigma} .$$

By the central limit theorem (Lehmann (1999)), the numerator of T_n converges in distribution to the normal random variable with mean 0 and variance 1, denoted by $N(0,1)$, and by the weak law of large numbers (Lehmann (1999)), the denominator of T_n converges in probability to $1 / \sqrt{2}$. Then by Slutsky's theorem (Lehmann (1999)), T_n converges in distribution to $\sqrt{2}\,N(0,1)$.

But

$$SMD_n = \frac{\overline{Z}}{s} = \frac{1}{\sqrt{n}} T_n .$$

So, for sufficiently large n,

$$SMD_n \approx \frac{\overline{2}}{\sqrt{n}} N(0,1),$$

where "≈" means the distribution of SMD_n is approximated by that of $\sqrt{\frac{2}{n}}N(0,1)$ for large n.

Simulation Results

Table 2. Mean and Standard Deviation of SMD_{200}* Under No Up-Front Matching and Up-Front Matching

	No Up-Front Matching		Up-Front Matching	
Variables	Mean SMD_{200}	Standard Deviation of SMD_{200}	Mean SMD_{200}	Standard Deviation of SMD200
Number of anti-psychotics prescribed	0.446	0.103	0.042	0.079
Age at index date, years	-0.045	0.099	-0.015	0.097
Number of psychiatric hospitalizations	0.133	0.108	-0.082	0.093
Number of psychiatric drugs prescribed	0.085	0.101	-0.000	0.094

*: Standardized mean difference based on samples of size 200 across 500 studies.

Simulation Results

Table 3. Aggregated Mean Scores Using Means from Each of the 500 Simulated Studies

	No Up-Front Matching Aggregated Means		Up-Front Matching Aggregated Means	
Variables	IAP (n=200)	OAP (n=200)	IAP (n=200)	OAP (n=200)
Number of anti-psychotics prescribed	1.774	1.233	1.756	1.702
Age at index date, years	37.970	38.580	38.050	38.250
Number of psychiatric hospitalizations	0.716	0.563	0.738	0.848
Number of psychiatric drugs prescribed	3.997	3.752	3.986	3.988

Note: Aggregated means under the up-front matching algorithm are identical between treatment groups for each covariate and are essentially equal to the aggregated means for the IAP group under no up-front matching.

Simulation Results

Table 3. Aggregated Mean Scores Using Means from Each of the 500 Simulated Studies

Variables	No Up-Front Matching Aggregated Means		Up-Front Matching Aggregated Means	
	IAP (n=200)	OAP (n=200)	IAP (n=200)	OAP (n=200)
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Age at index date, years	37.970	38.580	38.050	38.250
Number of psychiatric hospitalizations	0.716	0.563	0.738	0.848
Number of psychiatric drugs prescribed	3.997	3.752	3.986	3.988

Note: Aggregated means under the up-front matching algorithm are identical between treatment groups for each covariate and are essentially equal to the aggregated means for the IAP group under no up-front matching.

Table 1.b - Summary of Propensity Score Covariates in Claims Database - Simulation Database

Variables	IAP (n=2620)		OAP (n=11051)		Standardized Difference in Means*
	Mean	Variance	Mean	Variance	
Number of anti-psychotics prescribed	1.78	1.54	1.23	1.41	0.451
Age at index date, years	37.97	173.77	38.57	194.58	-0.044
Number of psychiatric hospitalizations	0.72	1.52	0.56	1.39	0.129
Number of psychiatric drugs prescribed	4.00	7.95	3.74	8.45	0.089

IAP: injectable atypical anti-psychotics; OAP: oral atypical anti-psychotics.
*: The difference in the means (IAP minus OAP) divided by the square root of the average of the variance in the 2 groups.

Conclusions and Remarks

- Our simulation illustrates a major benefit of up-front matching: it creates populations of patients whose balance on the covariates for which matching was implemented is comparable to what would be achieved with randomization.

- Although up-front matching is based on only a subset of covariates, it is anticipated that it will provide a database that enables more robust and efficient estimates of treatment effect than using no matching at enrollment.

- These benefits are desirable even in POS's not intended for regulatory purposes but will be even more valuable for studies whose results become part of the evidence for regulatory decision making – their results will be more credible and there is the potential for significant efficiency in generating the data.

- In addition to potential efficiency gains based on balance there is the real possibility that the percentage of patients not in the common support will be relatively substantial, and the cost savings in not following such patients in a POS could be substantial.