Real World Data and Real World Evidence: Challenges and Opportunities Panel Discussion

Committee on Developing a Framework to Address Legal, Ethical, Regulatory, and Policy Issues for Research Specific to Pregnant and Lactating Persons, Meeting #3

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"Concerns regarding both the limited generalizability and the slow pace of traditional randomized trials have led to calls for greater use of real-world evidence (RWE) in the evaluation of new treatments or products. The RWE label has been used to refer to a variety of departures from the methods of traditional randomized controlled trials."

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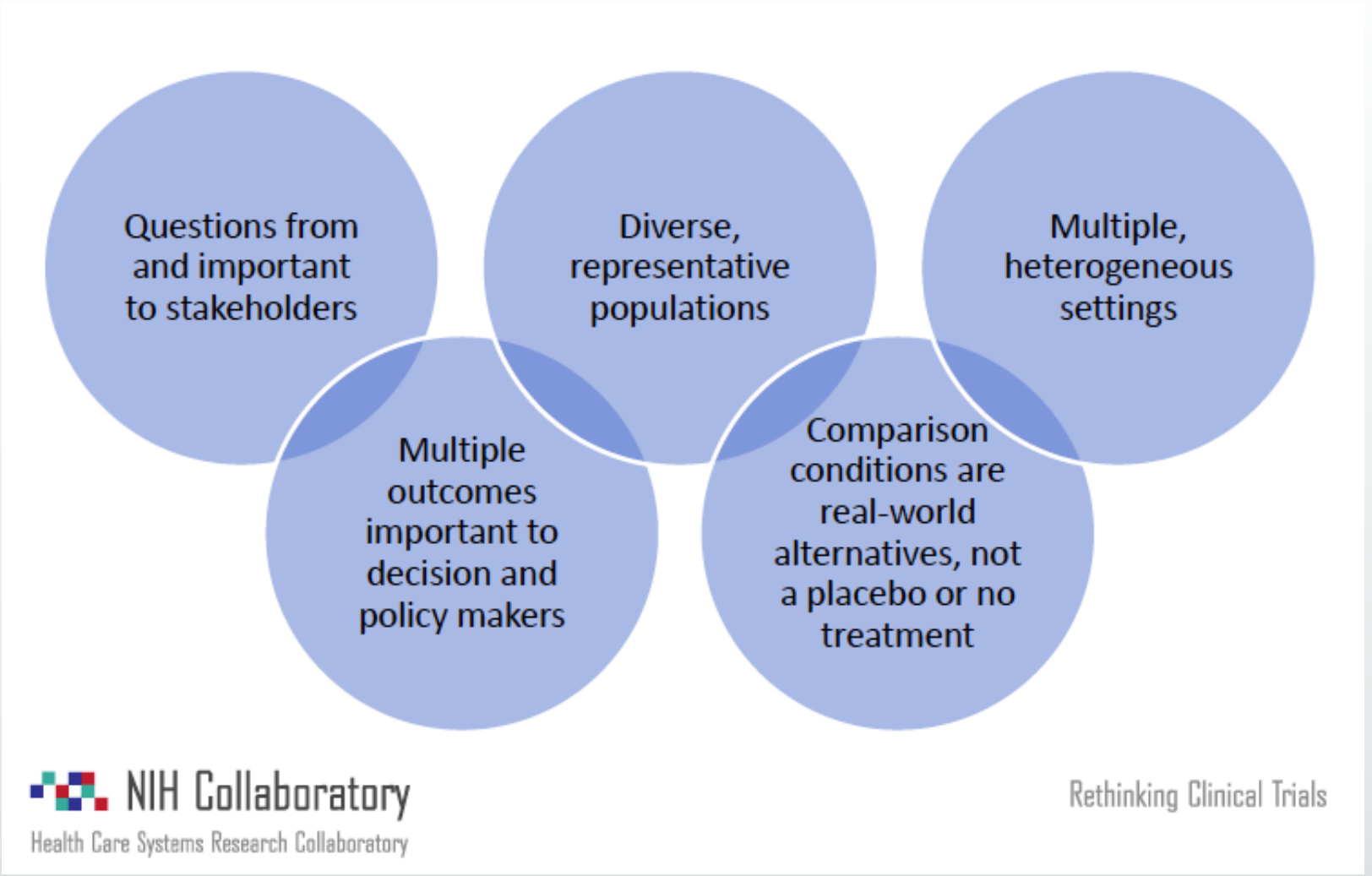


Sources of real-world data include Pragmatic clinical trials, registries, electronic health record data, administrative claims, validated population level surveys, mhealth, digital technologies, other observational data

PCTs: Fewer exclusions allow for a broader subset of participants

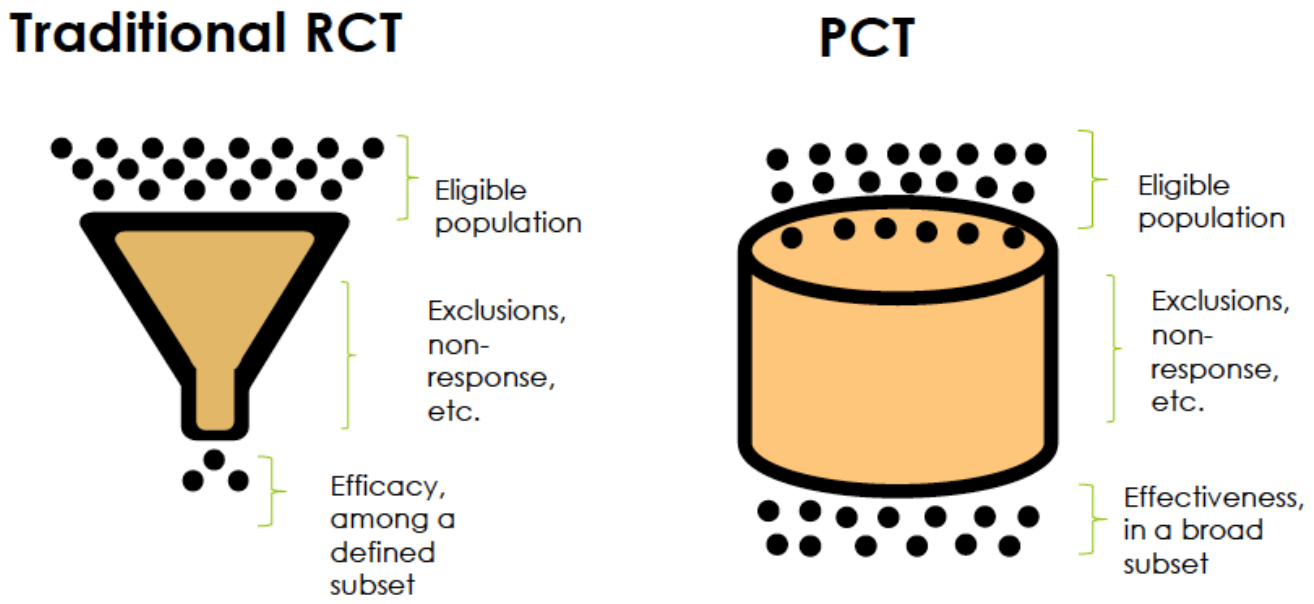


Figure provided by Gloria Coronado, PhD, Kaiser Permanente Center for Health Research

- In many scenarioes, RWD will be the only source of data available for inference
  - Pregnant women were not in the Pfizer/Biontech and Moderna COVID vaccine trials)
  - Single-armed trials
  - Multimorbid, polypharmacy patients often excluded from trials

Women under-represented in studies that were utilized for coverage determinations that impacted their group

"Participants in cardiovascular studies relied on by the CMS for coverage determinations differ substantially from the Medicare population. Data frequently are not available on relevant subgroup populations….need for data more relevant to Medicare beneficiaries by increasing enrollment of, and reporting on, women and elderly individuals in clinical trials and use of relevant data for coverage decisions."

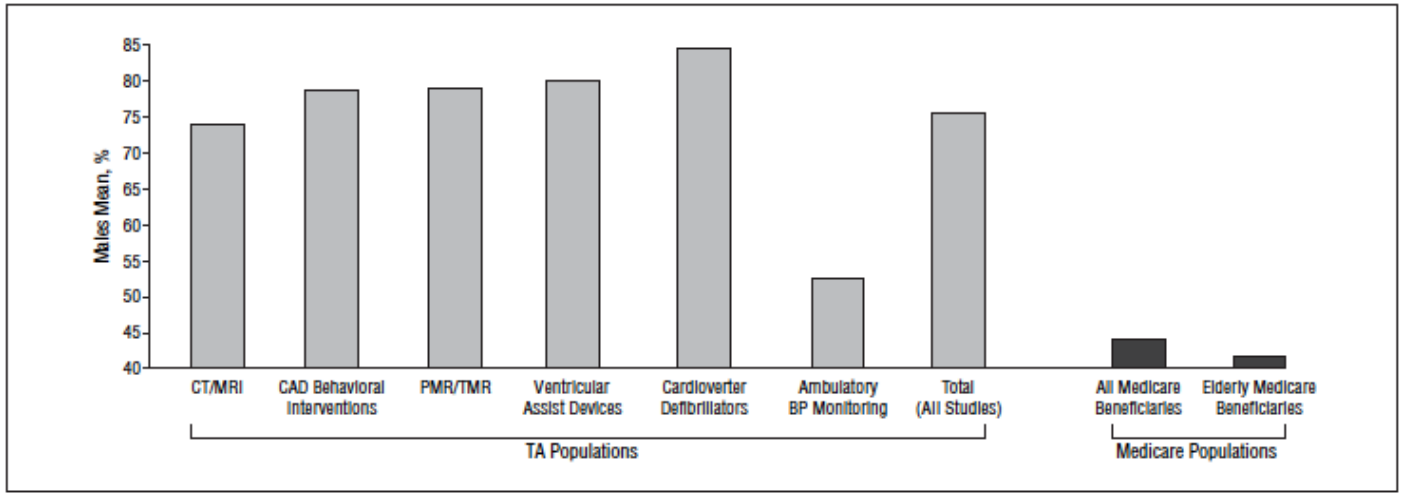
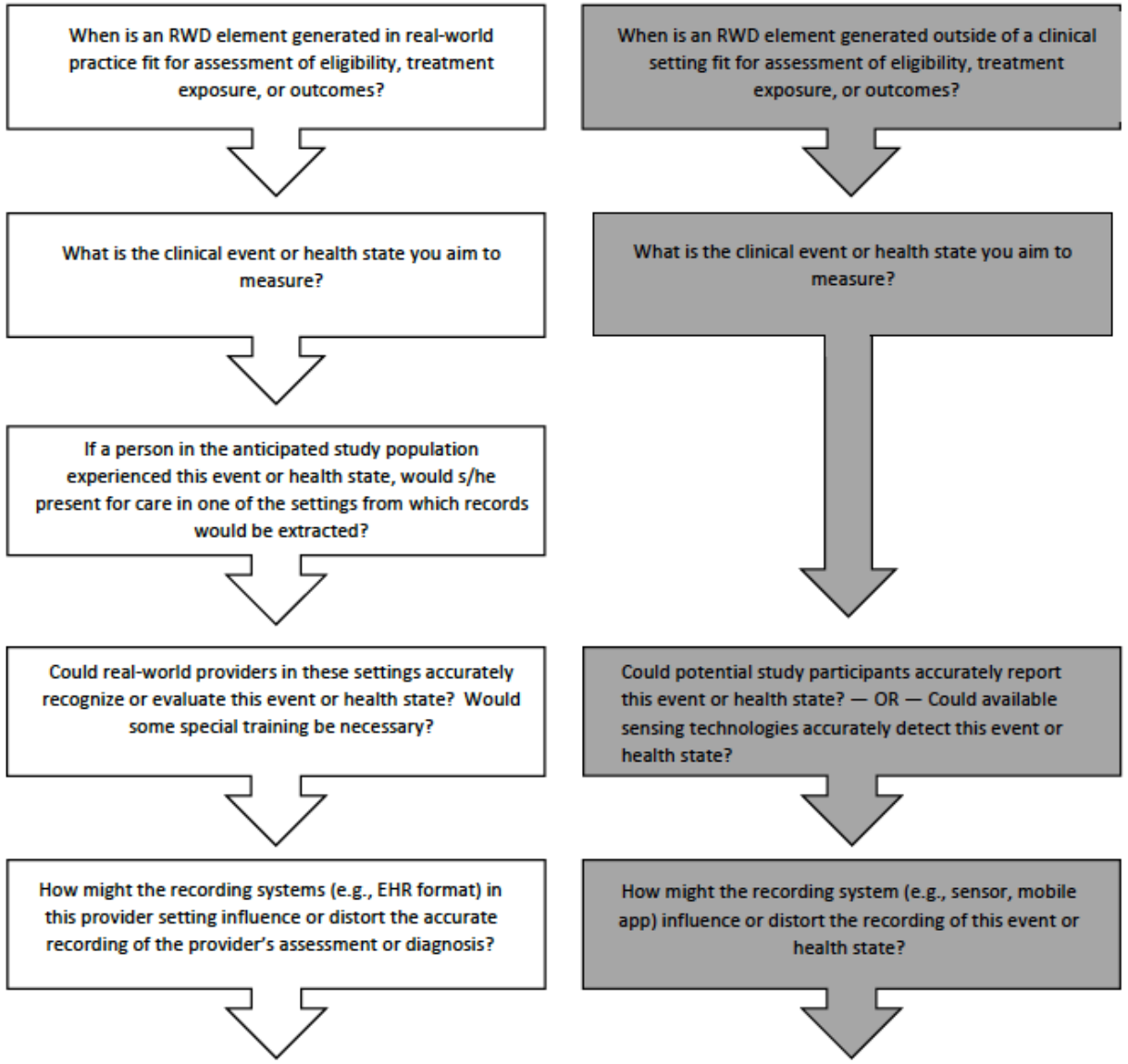
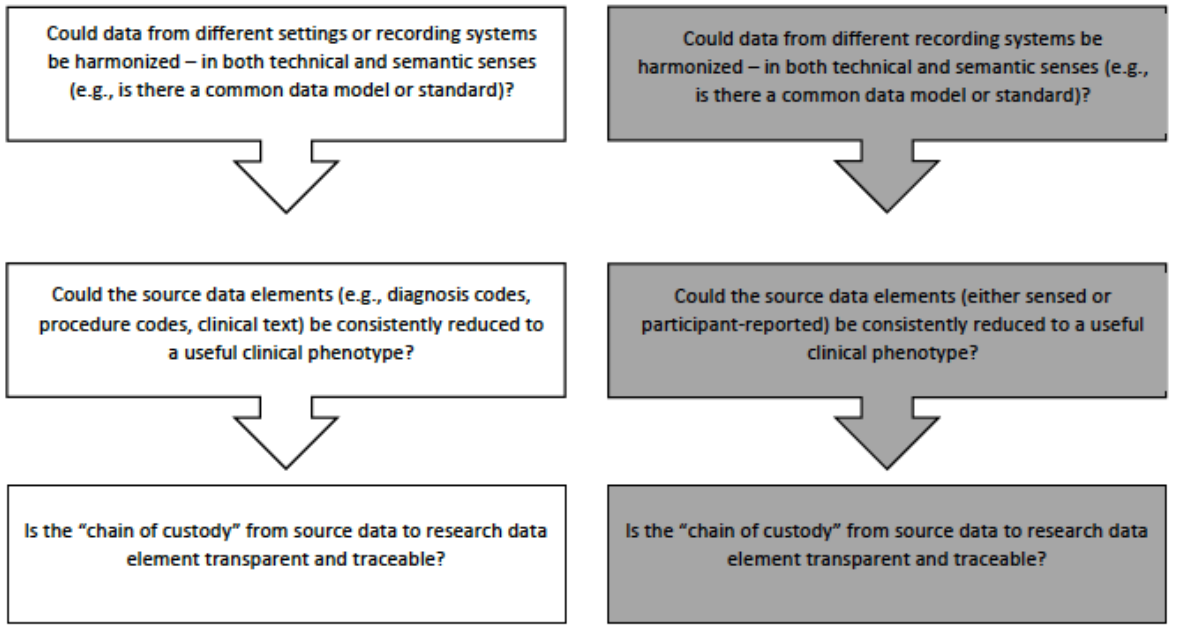


Figure 2. Mean percentage of males in technology assessment (TA) study populations compared with Medicare beneficiary populations. BP indicates blood pressure; CAD, coronary artery disease; CT, computed tomography; MRI, magnetic resonance imaging; PMR, percutaneous myocardial revascularization; and TMR, transmyocardial revascularization.

When is a Real-World Data Element Fit for Assessment of Eligibility, Treatment Exposure, or Outcomes?

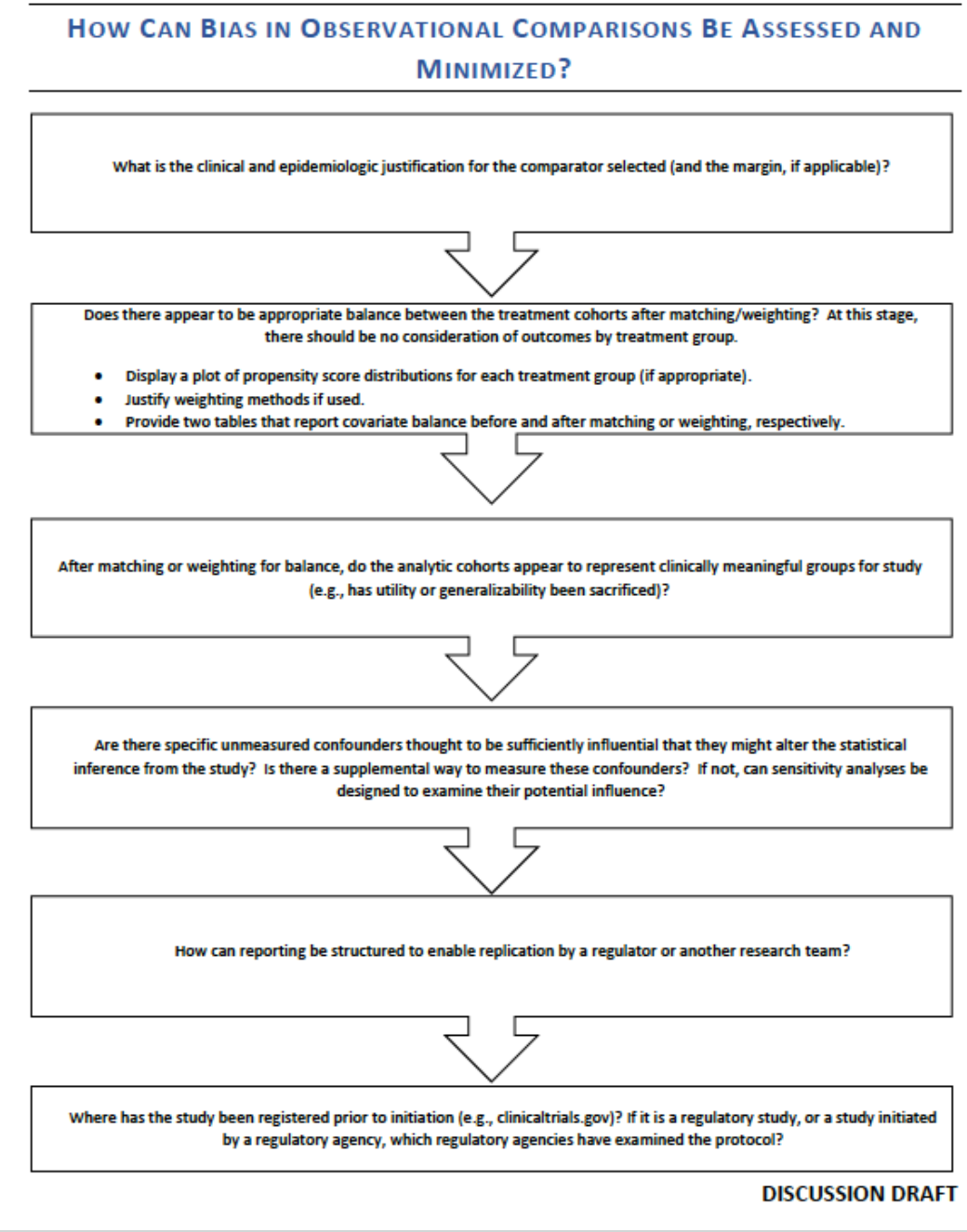


When is a Real-World Data Element Fit for Assessment of Eligibility, Treatment Exposure, or Outcomes?, Continued



National Academies of Sciences, Engineering, and Medicine. 2019. Examining the impact of real-world evidence on medical product development: Proceedings of a workshop series. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/25352.

Workshop 3: Application



- Upside is more relevant, generalizable findings using real-world data (power, sub-groups, actual user populations, recency, speed)
- Downside is more deliberate study design and methods must be applied to limit bias for valid inference (ie. Addressing confounding)
- Challenges of data harmonization (eg. claims databases are organized by payer. Delineating child's data from parent and linkage is not always straight forward)
- More deliberate quality control approaches at each phase (exploratory data analysis, informative missingness considerations, unmeasured confounding)

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Workshop 3: Application

PROCEEDINGS OF A WORKSHOP SERIES

Examining the Impact of Real-World Evidence on Medical Product Development

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REVIEW

When Can Nonrandomized Studies Support Valid Inference Regarding Effectiveness or Safety of New Medical Treatments?

Jessica M. Franklin[1,2,*], Richard Platt[3], Nancy A. Dreyer[4], Alex John London[5], Gregory E. Simon[6], Jonathan H. Watanabe[7], Michael Horberg[8], Adrian Hernandez[9] and Robert M. Califf[10]

The randomized controlled trial (RCT) is the gold standard for evaluating the causal effects of medications. Limitations of RCTs have led to increasing interest in using real-world evidence (RWE) to augment RCT evidence and inform decision making on medications. Although RWE can be either randomized or nonrandomized, nonrandomized RWE can capitalize on the recent proliferation of large healthcare databases and can often answer questions that cannot be answered in randomized studies due to resource constraints. However, the results of nonrandomized studies are much more likely to be impacted by confounding bias, and the existence of unmeasured confounders can never be completely ruled out. Furthermore, nonrandomized studies require more complex design considerations which can sometimes result in design-related biases. We discuss questions that can help investigators or evidence consumers evaluate the potential impact of confounding or other biases on their findings: Does the design emulate a hypothetical randomized trial design? Is the comparator or control condition appropriate? Does the primary analysis adjust for measured confounders? Do sensitivity analyses quantify the potential impact of residual confounding? Are methods open to inspection and (if possible) replication? Designing a high-quality nonrandomized study of medications remains challenging and requires broad expertise across a range of disciplines, including relevant clinical areas, epidemiology, and biostatistics. The questions posed in this paper provide a guiding framework for assessing the credibility of nonrandomized RWE and could be applied across many clinical questions.

The randomized controlled trial (RCT) has been the gold standard for evaluating the effectiveness and safety of medications for more than 50 years.[1] Despite the many advantages of traditional RCTs, there are concerns that the narrowly defined patient population and tightly controlled treatments and settings required in many RCTs for drugs may not reflect treatment effects or outcomes in usual care. In addition, the high costs of both implementation and long-term follow-up in a traditional RCT often constrain the focus to outcomes that can be measured in the shorter term with smaller sample sizes, including intermediate outcomes, biomarkers, or surrogates. For these reasons, real-world evidence (RWE) has been proposed as a complementary source of evidence that can better capture treatments as used in routine care and the subsequent outcomes that are most meaningful to patients.[2,3] RWE has been defined as any evidence regarding the risks and benefits of medications derived from data sources other than traditional RCTs, i.e., real-world data (RWD).[4,5] Under this definition, RWE can be either randomized or nonrandomized.

Randomly allocating treatment to study patients ensures that, on average, treatment groups will be similar with respect to all patient characteristics that may impact risk for the outcome.[6] The resulting balance in patient characteristics enables one to infer that differences in outcomes between treatment groups can be attributed to differences in the treatments under study, rather than other factors. Nonrandomized or observational studies, in contrast, do not use random treatment allocation. As patients and their providers make treatment decisions on the basis of individual patient characteristics and circumstances, patients receiving alternative therapies may differ on many important factors affecting outcomes. While confounders known to influence both treatment assignment and outcomes can be measured and adjusted for in the design or analysis of nonrandomized studies, it can never be guaranteed that all such confounding factors have been controlled. There is always a possibility that there were additional factors unknown to the investigators that may be confounding the observed relationships between treatments and outcomes, leading to inaccurate estimates of treatment effects.

Given the strong control of both known and unknown confounding factors that is a benefit of randomization, why pursue the use of nonrandomized RWE for informing treatment decision

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REVIEW

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WHITE PAPER

When Can We Rely on Real-World Evidence to Evaluate New Medical Treatments?

Gregory E. Simon[1,*], Richard Platt[2], Jonathan H. Watanabe[3], Andrew B. Bindman[4], Alex John London[5], Michael Horberg[6], Adrian Hernandez[7] and Robert M. Califf[8]

Concerns regarding both the limited generalizability and the slow pace of traditional randomized trials have led to calls for greater use of real-world evidence (RWE) in the evaluation of new treatments or products. The RWE label has been used to refer to a variety of departures from the methods of traditional randomized controlled trials. Recognizing this complexity and potential confusion, the National Academies of Science, Engineering, and Medicine convened a series of workshops to clarify and address questions regarding the use of RWE to evaluate new medical treatments. Those workshops identified three specific dimensions in which RWE studies might differ from traditional clinical trials: use of real-world data (data extracted from health system records or data captured by mobile devices), delivery of real-world treatment (open-label treatments delivered in community settings by community practitioners), and real-world treatment assignment (including nonrandomized comparisons and variations on random assignment such as before-after or stepped-wedge designs). For any RWE study, decisions regarding each of these dimensions depends on the specific research question, characteristics of the potential study settings, and characteristics of the settings where study results would be applied.

Traditional randomized clinical trials (TRCTs) often fail to provide the timely and relevant evidence necessary for regulatory, clinical, and coverage decisions regarding use of novel medical treatments or new uses for existing treatments.[1,2] Participants in TRCTs often differ markedly from those treated in community practice in terms of sociodemographic characteristics, prognostic characteristics, co-occurring conditions, and motivation or likelihood of treatment adherence. The tightly controlled (and typically blinded) treatments in TRCTs may yield outcomes quite different from outcomes of more typical treatment by real-world providers. Relatively small sample sizes sometimes limit TRCTs to assessment of intermediate or surrogate outcomes (e.g., tumor shrinkage or reduction in suicidal ideation), rather than the outcomes of greatest interest to patients, clinicians, and purchasers (e.g., cancer-free survival or prevention of suicidal behavior). Concerns regarding the relevance and generalizability of findings from TRCTs have prompted demands for evidence derived from real-world settings.[2,3]

Efficiency of evidence generation is also a growing concern. Tightly controlled treatment delivery and research-specific data collection contribute significantly to the increasing costs of TRCTs, with the median cost of a phase III clinical trial exceeding $100 million[3] and the mean development cost of bring a new medication to market exceeding $1.3 billion.[4] Those rising costs threaten to slow or restrict development of innovative treatments, novel usages of established treatments, and efficient comparative effectiveness trials.[3,5] Narrow eligibility criteria and demanding assessment protocols slow recruitment, delaying or completely preventing trial completion because of inadequate recruitment.[3,6]

The COVID-19 pandemic has dramatically revealed the need for more efficient and timely evidence generation. The urgent need for evidence regarding new and re-purposed therapeutics for COVID-19 has prompted both refreshing innovation to improve speed and efficiency[9,10] and frustration regarding the fragmentation and slow pace of traditional clinical trials initiated during the pandemic.[11,12]

Mindful of the need for more relevant evidence and more efficient evidence generation, the US Food and Drug Administration (FDA) sponsored a three-part workshop series, organized and hosted by the National Academies Forum on Drug Discovery, Development, and Translation on "Examining the Impact of Real-World Evidence on Medical Product Development." As described in recently published proceedings,[13] those workshops focused on aligning incentives to promote appropriate innovation and developing practical approaches to improve the efficiency and relevance of evidence generation. As participants in that workshop series, we now propose specific, practical guidance based on our discussions during and following those workshops.

Dimensions of RWE

As others have pointed out,[2,14] real-world evidence (RWE) may be best defined by what it is not. By that definition, RWE could include a range of evidence not generated by TRCTs.[14] Recent discussion by the FDA defines RWE as evidence derived from real-world data (RWD) rather than data collected by and for research. Studies to

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REVIEW

When Are Treatment Blinding and Treatment Standardization Necessary in Real-World Clinical Trials?

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Concerns regarding both the limited generalizability and the slow pace of traditional randomized trials have led to calls for greater use of real-world evidence in the evaluation of new treatments or products. Real-world clinical trials or pragmatic trials often differ from traditional clinical trials in the use of open-label or nonblinded treatments delivered by real-world clinicians in community practice settings. Blinding and standardization of treatment may sometimes be necessary for internal validity, but they may also obscure or distort meaningful differences between treatments. When investigators consider whether blinding of clinicians, patients, or assessors is necessary, we suggest they consider several specific questions: Will clinicians, patients, and assessors have expectations or preferences regarding benefits or adverse effects? How might those expectations affect treatment uptake, treatment adherence, or assessment of outcomes? Will expectations differ in the settings where trial results will be applied? How would blinding of treatment reduce biases? How would blinding obscure true differences between treatments? How would procedures necessary for blinding reduce acceptability or increase risk of trial participation? When investigators consider how strictly treatments should be standardized, we suggest they consider several specific questions: How would treatment effectiveness or safety vary according to clinician experience or expertise? What level of experience or expertise is available in potential trial settings and settings where trial results would be applied? Is some level of standardization necessary for valid inference? Considering any special vulnerabilities of the study population, is some level of standardization necessary to assure participant safety?

Although traditional randomized trials remain the gold standard for assessing efficacy and safety of novel treatments, the slow pace and uncertain generalizability of traditional trials have prompted a growing interest in real-world evidence (RWE), including pragmatic or real-world clinical trials conducted in community settings.[1–3] Recognizing the need both for more relevant evidence and a far more efficient evidence-generating process, the National Academies of Science, Engineering, and Medicine Forum on Drug Discovery Development and Translation[4] organized a series of workshops sponsored by the US Food and Drug Administration focused on Examining the Impact of Real-World Evidence on Medical Product Development.[5] Those workshops considered specific dimensions in which RWE studies might differ from traditional clinical trials: use of real-world data, less standardized treatment delivered by community providers, and assignment of treatments by some mechanism other than individual randomization. Expanding on these considerations, there are certain features that distinguish traditional clinical trials from real-world clinical trials or pragmatic trials. In traditional trials, study participant eligibility follows stringent criteria that restricts to patients likely to have the outcome of interest, likely to be responsive to the experimental intervention, and likely to adhere to treatment protocols. Conversely, pragmatic trials will include all participants with a growing interest in real-world evidence (RWE), including pragmatic or real-world clinical trials conducted in community settings.[1–3] Recognizing the need both for more relevant evidence and a far more efficient evidence-generating process, the National Academies of Science, Engineering, and Medicine Forum on Drug Discovery Development and Translation[4] organized a series of workshops sponsored by the US Food and Drug Administration focused on Examining the Impact of Real-World Evidence on Medical Product Development.[5] Those workshops considered specific dimensions in which RWE studies might differ from traditional clinical trials: use of real-world data, less standardized treatment delivered by community providers, and assignment of treatments by some mechanism other than individual randomization. Expanding on these considerations, there are certain features that distinguish traditional clinical trials from real-world clinical trials or pragmatic trials. In traditional trials, study participant eligibility follows stringent criteria that restricts to patients likely to have the outcome of interest, likely to be responsive to the experimental intervention, and likely to adhere to treatment protocols. Conversely, pragmatic trials will include all participants with the condition of interest regardless of predicted risk, estimated responsiveness, or adherence likelihood. Traditional clinical trials apply meticulously specified experimental interventions with experienced practitioners in settings selected predicated on expertise with patients enrolled in the study. Pragmatic trials will include practitioners across the spectrum of usual care and in the full range of clinical settings. Whereas in traditional clinical trials, the comparison intervention will be narrowly defined and may include a placebo, pragmatic trials will use a comparison that resembles usual care or best alternative treatment approach.[6]

As participants in the aforementioned workshop series, we here discuss two questions prominent in those discussions: When is concealment or blinding of treatment assignment necessary? How strictly should treatment quality or intensity be standardized? Both questions involve "real-world" adaptations of traditional practice in clinical trials: open-label treatment and allowing natural variation in quality or intensity of treatment. For each of these questions,

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