Improving Patient Subgroup Representation with Real-World Data

Real World Efficacy and Patient Subgroups

Duke
MARGOLIS CENTER *for* Health Policy

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Executive Summary

Real world data (RWD), or patient-level data generated outside of traditional clinical trial settings, has enabled the development and use of real-world evidence (RWE) that is generated and increasingly used in pragmatic trials, externally controlled trials, and observational studies. Subgroups, or subsets of patients with specific clinical or demographic characteristics, may be traditionally excluded from or otherwise unengaged in gold standard randomized clinical trials (RCTs) and could greatly benefit from RWD/E. Studies using RWD/E can enable inclusion of traditionally underrepresented subgroups as there are fewer barriers to research participation than RCTs. Underrepresentation of these subgroups limits the generalizability of research findings, reinforces treatment inequities, perpetuates data bias resulting from overestimations, and further excludes subgroups from benefits of the knowledge and innovation derived from research. Understanding the individual and/or combined influence of clinical and demographic characteristics among patient subgroups holds measurable value, especially in cases where such characteristics can be a proxy for observable variations in treatment effects.

In this paper, we describe opportunities for and challenges to leveraging RWD in order to estimate and measure treatment effects among and across patient subgroups. We also discuss important terminology considerations that accompany measurements of therapeutic effect in subgroups, supplementing clinical trials with RWD for subgroup analysis, leveraging RWD to address shortcomings in trial data, equitable solutions to address data missingness, and leveraging RWD to improve care among patient subgroups.

How This Paper Was Developed

This whitepaper was informed by a December 13-14, 2022 private workshop entitled, "Real World Efficacy: Patient Subgroups," and hosted by the Duke-Margolis Real-World Evidence Collaborative; by several regular working group and stakeholder calls with members of the collaborative; and by literature cited and summarized in this white paper (see **Appendix D**). Workshop participants included industry representatives, sponsors, research groups, data vendors, and patient advocacy groups, who provided insight and expert perspectives on real world efficacy and patient subgroups..

Background

A steady and growing availability of RWD, or individual-level patient and consumer data generated outside of clinical trial settings, has led to increasing reliance on RWE across pragmatic trials, externally controlled trials, and observational study settings aiming to address specific research questions concerning the therapeutic effects of treatment(s) administered to patients in real-world clinical settings.[1] Such reliance is especially true for evidence generation among subsets of patients with specific clinical or demographic characteristics, or subgroups that may be traditionally excluded from or otherwise unengaged in RCTs. Studies that leverage fit-for-purpose RWD are, therefore, useful to investigate and measure on-label or off-label treatment effects and safety outcomes that might differ in patient subgroups and therefore, warrant different clinical approaches to treat and clinically manage these patients in real-world settings.

However, certain challenges accompany uses of RWD for subgroup analyses. First, in cases where a subgroup is particularly small, low statistical power may result and lead to:

- False and/or overestimated treatment effects among patient subgroups,

- Increased patient heterogeneity that is often inherent to RWD, and/or
- Measurement and confounding bias resulting from secondary uses of RWD.

Second, though RCTs are the gold standard for examining cause-effect relationships between interventions and outcomes, they are accompanied by misleading assumptions. One important assumption inherent to RCTs is that confounding factors are uniformly distributed across the two groups by virtue of the randomization process, thus overlooking external generalizability and validity.[2] Third, randomization procedures used within RCTs do not adequately account for consequential patient dimensions that are commonly filtered out by stringent exclusion criteria. Even with United States Food and Drug Administration (FDA) directives and guidelines,[3] clinical trial participants are often not representative of the larger general population.

Alongside these challenges are opportunities to understand the individual and/or combined influence of clinical and/or demographic characteristics among patient subgroups, especially in cases where such characteristics can be a proxy for observable variations in treatment effects. In this paper, we describe opportunities and challenges to leveraging RWD to estimate and measure treatment effects among and across patient subgroups. Importantly, we discuss terminology uses and considerations that accompany measures of therapeutic effect in real-world versus clinical trial settings, supplementing clinical trials with RWD for subgroup analysis, leveraging RWD to address data missingness, and improving care among patient subgroups. A greater research focus on the aforementioned topics can in turn can lead to the development of solutions that are informed by RWD/E to increase research inclusion of underrepresented groups.

Terminology Considerations

Researchers, industry, regulators, patients, and other key stakeholders stand to benefit from alignment around terms and definitions that are commonly used to describe variation in treatment effects among patients in real-world versus clinical trial settings. This alignment is a necessary first step to enable shared uses of terms, prevent potential misunderstandings, and promote collaboration among providers and researchers in practice. Lastly, standardized key terms would enable a shared understanding of how similar terms, like efficacy versus effectiveness and subgroups versus subpopulations, are alike and how they differ in research settings.

Efficacy vs. Effectiveness

Efficacy is defined as the performance of an intervention under ideal and controlled circumstances, whereas **effectiveness** refers to its performance under real-world conditions.[4] The U.S. Food and Drug Administration (FDA) further clarifies the distinction between these terms: efficacy refers to the findings in an adequate and well-controlled trial or the intent of conducting such a trial; effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.[5] Further, effectiveness is a term used within studies that examine interventions under circumstances that more closely approach real-world practice (i.e., "pragmatic" trials[6]), with more heterogeneous patient populations, less-standardized treatment protocols, and delivery in routine clinical settings.[7] Importantly, scientific rigor is not compromised in pragmatic trials that measure treatment effectiveness versus controlled "explanatory" trials that measure treatment efficacy under ideal conditions.

Efficacy is defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under real-world conditions.[4]

Subpopulation vs. Subgroup

A **subpopulation** describes a specific group of individuals with common characteristics (e.g., race and/or ethnicity, age, risk factors) that is the target of an intervention or a policy recommendation. Conversely, **subgroup** describes an analysis unit of a subset of participants (e.g., selected set of individuals with specific characteristics within an individual study or across studies in the case of individual patient data meta-analyses).[8] While a subpopulation is a group of individuals with common characteristics, a subgroup is an analysis of a set of individuals within a given study population. Often, these terms are used interchangeably and present challenges. Distinguishing between these terms allows researchers to more accurately assess the potential heterogeneity of treatment effects,[9] either by degree or direction, across distinguishable patient strata. Furthermore, potential for assessment errors exists in looking at treatment/outcomes among different study populations/groups without clear delineation between the subgroup and subpopulation.

While a subpopulation is a group of individuals with common characteristics, a subgroup is an analysis of a set of individuals within a given study population.

Table 1 summarizes and compares these key terms and offers important considerations and recommendations for practitioners and policymakers, respectively. **Appendix E** contains a glossary of definitions for these terms.

Table 1 Comparisons of Key Terms, Practical Considerations, and Policy Recommendations for Real-World Evidence Studies Examining Real-World Efficacy

Key Term Comparison	Practical Consideration(s)	Policy Recommendation
Efficacy vs. Effectiveness	Scientific rigor should be applied regardless of whether efficacy or effectiveness are being measured.[10] This distinction also is important because there are many factors that might impact whether or not a particular intervention is effective, apart from whether an intervention is efficacious. These factors include access to and adherence to interventions.[11]	Researchers should abide by FDA definitions of efficacy and effectiveness when conducting trials.
Subpopulation vs. Subgroup	The distinction between these terms allows researchers to effectively assess the potential heterogeneity of treatment effects by degree or direction across different patient populations.[12] Without this distinction, an opportunity exists for assessment errors in looking at treatment/outcomes among different study populations/groups. This distinction allows treatment effect variation by levels of a baseline factor (e.g., age, race, sex).	Researchers should focus on a specific unit of analysis and not use subgroup/ subpopulation interchangeably when conducting studies.

Real-World Efficacy and Patient Subgroups

Real-world efficacy refers to the efficacy of a particular treatment in real-world settings, rather than in the controlled conditions of a clinical trial. **Patient subgroups** are disaggregated groups of patients with shared characteristics, such as age, gender, race and/or ethnicity, comorbidities, and single or multiple gene variations.[13] Patient subgroups may have different responses to treatment due to differences in underlying pathophysiology, genetics, social determinants of health, and other factors, including social determinants of health. Real-world studies that assess subgroups typically explore differences in treatment outcomes among predefined subgroups, corresponding with a specific question of interest (e.g., subgroups by race/ethnicity when examining heterogeneity of effects by adverse social determinants of health), including patient-reported and patient-functional outcomes.

Patient subgroups are disaggregated groups of patients with shared characteristics, such as age, gender, race and/or ethnicity, comorbidities, and single or multiple gene variations.

Using RWD to Supplement Clinical Trials for Subgroup Analysis

RWE studies are useful to compare the real-world efficacy of novel treatments used for on-label purposes to either on- or off-label treatments.[14] RWE studies also are useful to identify treatment outcomes that are compelling enough to further investigate or support label-expansion(s).[15]

Further, RWD/E may be useful to address common subgroup analysis constraints that may stem from a lack of subgroup diversity in clinical trials. Such lack of diversity could result from several health system factors that include but are not limited to patient under-engagement or disengagement, lack of access to health systems, study selection bias, and consent bias. RWD/E, when sufficiently robust, has the propensity to fill knowledge gaps related to the long-term safety and real-world efficacy of treatments among and across patients that may be at a relatively higher risk of poor treatment outcomes due to distinct biological, environmental, discriminatory, or demographic factors. Indeed, the incorporation of RWD/E plays a significant role in systematically identifying treatment contraindications and providing longitudinal data on treatment outcomes for groups that are, both historically and, presently, challenged to engage and retain in clinical research.[16]

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Figure 2 Challenges in Leveraging RWD/E for Subgroup Analysis

- Lack of structured and unstructured data standardization
- Variations in data quality and accuracy
- Variability in demographic stratification methods
- Challenges associated with accessing RWD/E data sources
- Limited acceptance of RWD/E sources within regulatory contexts[17]

Altogether, these challenges could limit the utility of RWD/E as a primary method to address sampling challenges in clinical trials. Without careful consideration and proper study design methods, RWD/E can introduce or exacerbate sampling bias and perpetuate statistical error.[18] Yet, if these challenges are addressed by gaining reliable and relevant RWD sources, study designs, and statistical methods, RWE studies can provide useful insights about subgroups within and across heterogenous patient populations. Industry and health system stakeholders with a mission to increase patient demographic diversity in clinical research should leverage RWD/E to bridge critical evidence gaps in populations that are understudied and underrepresented in clinical research. When leveraged appropriately, RWD could be an important supplement to improve clinical trial dataset diversity that is typically required for reliable subgroup analyses.

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Methodological Challenges and Opportunities

Several challenges accompany uses of RWD/E to assess real-world efficacy among patient subgroups. First, given that RWD/E studies typically assess secondary data, four important issues may arise:

- Secondary data selection use may lead to inaccurate assumptions about exposures and outcomes of interest,
- Differential recall bias that can be inherent to certain RWD sources,
- Measurement errors in attempts to assign RWD endpoints to a real-world estimand,[19] and
- Differential or residual confounding and heterogeneity in treatment effect may become conflated.[20]

One such challenge for researchers is determining whether they should select secondary data sources that are specific to patient populations with known clinical, demographic, and/or behavioral characteristics, such as acute care patients within a specific geographic region who might not return for follow-up care or seek more care than the average population of interest. In such an instance, selection bias may result since patient selection in the study is not random. Also, although differential recall bias can be inherent to some RWD sources, such as electronic health records (EHRs), recall bias may perpetuate upon attempts to address missing values that may provide estimates of total, direct, and indirect effects .[21]

Measurement errors[22] also may arise when assigning primary endpoints to real-world estimands[23] (see **Appendix E: Glossary**), especially in cases where an independent endpoint adjudication committee is not used to ensure the relevance, validity, and reliability of those primary endpoints. Lastly, in RWE study settings, such as observational studies, challenges exist in determining correlation between differential or residual confounding patterns from heterogeneity in treatment-effect patterns.[24] Addressing these specific challenges by utilizing high-quality RWD/E sources, appropriate study designs, and statistical methods may allow for greater use of RWD/E to assess real-world efficacy across subgroups.

Another notable challenge is that RWE studies testing multiple hypotheses or comparisons through post-hoc RWD analyses may be susceptible to inflated results and type 1 statistical error due to confounding bias. In particular, if patient populations are chosen for post-hoc analyses based on their likelihood to benefit from the treatment intervention that is under investigation, inflated positive test results can occur. Therefore, study designs with prespecified protocols and clearly defined real-world endpoints (i.e., real-world exposures and outcomes of interest) are key to reduce the likelihood of inflated results and type 1 statistical errors, and validate—internally and externally--real-world efficacy and outcomes in post-hoc studies using RWD.[25]

Other methodological issues may emerge in hybrid studies that leverage both RCT and external control arm data to assess real-world efficacy across patient subgroups, such as balancing measured confounders. In this case, balancing measured confounders among larger study cohorts does not necessarily imply balance across subgroups and may lead to confounding errors. Propensity score matching and other methods (e.g., re-weighting or re-estimation of propensity scores within subgroups) for confounding control can help to mitigate this issue. Also, the target trial framework can be used with appropriate statistical methodologies, such as covariate adjustment, to generate reliable insights into real-world efficacy among patient subgroups.[26] Nested design studies also can be used for the same purpose, which allow researchers to extend inferences of randomized trials to different populations to generalize results.[27]

Clinical Trial Diversity Planning and Engaging Underrepresented Groups

Extensive literature shows that certain demographics of patients are overwhelmingly underrepresented in clinical research, largely including racial and ethnic minorities, sexual and gender minorities, and pregnant and lactating persons.[28] Such underrepresentation limits the generalizability of research findings, reinforces treatment inequities, perpetuates bias resulting from overestimations, and further excludes underrepresented groups from benefiting from the knowledge and innovation derived from research.

These challenges are also seen in research exploring the real-world efficacy of more personalized treatments among biological subgroups (i.e., positive/negative biomarker status), whereas random high bias may occur if effect sizes are overestimated due to an overrepresentation any biological subgroup.[29]

Additionally, broader challenges exist to achieve clinical trial diversity using RWD. First, no nationally or internationally enforced regulatory standard exists to categorize racial/ethnic subgroups to observe and estimate treatment effect.[30] Second, perspectives among scientific experts examining race/ethnicity may be influenced by their cultural notions as a biological versus social construct. This bias also could be true for sex, gender identity, and sexual orientation, for which data are often inadequately assessed, collected, and reported. Also, although residence can be strong predictor of disease risk in the real-world, it is not often considered as a factor to assess treatment effect. Lastly, given certain administrative difficulties or political challenges to generating, reporting, and accessing RWD/E within underdeveloped countries and/or regions globally, leveraging such data for RWD/E studies may be impossible. Addressing these challenges to facilitate relevant and reliable subgroups analyses using RWD/E that are acceptable to regulators will require ongoing efforts towards harmonization of RWD/E standards, stronger data governance, and mechanisms for secure and trusted data linkage and tokenization.

High quality RWD collection and RWE generation is possible both through trustworthy and transparent engagement among health research stakeholders throughout the clinical research process.

To generate high-quality RWE on real-world efficacy among diverse patient subgroups, RWD quality is perhaps the most important factor to consider. High quality RWD collection and RWE generation is possible both through trustworthy and transparent engagement among health research stakeholders throughout the clinical research process. This engagement is especially, but not exclusively, needed for socially and economically marginalized patients and patients belonging to subgroups that have been subjected to clinical research misconduct and/or abuse. Trial design also is an important factor to consider, as study inclusion and exclusion criteria may inadvertently exclude patients with clinical comorbidities that are frequently observed among demographic subgroups with high disease

burden. Study inclusion and exclusion criteria based diagnostic measures that involve race-correction[31] (e.g., bone density scan, glomerular filtration rate, etc.), also might exclude patients inadvertently whose biological characteristics (e.g., genetic ancestry) may play a larger role in diagnostic algorithms.[32]

Currently, race and ethnicity often are used as primary stratification dimensions across health care, health science research, and clinical trial settings in the U.S. However, more acknowledge that race and/or ethnicity are social constructs that are predominantly used as proxies for various social and economic risk factors that have well-researched health impacts.[33] However, the routine collection of race and/or ethnicity across health care and research contexts is not a universal practice around the world, largely due to the prevalence of racial homogeneity across many countries. Extant research has demonstrated that there is no biological basis to race or ethnicity, further complicating debates on the utility of these constructs as a method of stratification across health research contexts. Regardless, rigor and transparency in reporting should exist with respect to how race/ethnicity (if documented) was determined (e.g., self-reported versus documented from Medicare enrollment data).

RWD/E may be a strategy to broaden inclusion criteria and limit unnecessary or scientifically unsubstantiated exclusion criteria, which could diversify patient cohorts to more accurately assess treatment effects among subgroups and reduce the likelihood of any biases in observable treatment effects. RWD/E also may be an effective strategy to model treatment effects by overlaying population diversity density with density among patients who have a higher probability of meeting inclusion and exclusion criteria.[34]

In their latest draft guidance, FDA encouraged trial sponsors to adopt strategies that help them expand beyond race as a single measure of subgroup diversity and consider characteristics such as sex, gender, sexual orientation, biomarker status, age, socioeconomic status, disability status, pregnancy/lactation status, mental health status, and many additional factors.[35] Moreover, FDA mentioned that trial sponsors' race and diversity plans should include an overview of the disease/condition in certain racial/ethnic groups, scope of medical product development, goals for enrollment of underrepresented racial and ethnic participants, and a specific plan of action to enroll and retain diverse participants. Trial sponsors, therefore, should create opportunities to learn from local health care providers and community leaders and establish recruitment sites in areas with high diagnosed and undiagnosed disease prevalence and penetrance among target subgroups. In this same vein, trial sponsors also could collaborate with public and private payors' analytics teams to identify and reach patients whose health outcomes are largely compounded by multiple social determinants of health needs that are unmet.

Leveraging ex-U.S. RWD for Subgroup Analysis

Ex-U.S. RWD (RWD collected outside of US contexts) is recognized by regulators, including the FDA, as a resource to either supplement or augment clinical trial datasets and address patient subgroup sampling deficits, statistical analysis limitations, and RCT trial design challenges. Ex-U.S. RWD became particularly attractive during the emergence of the COVID-19 pandemic, when little evidence existed based on observational data about the full scope and nature of the infection and its sequela. In addition, ex-U.S. RWD has been used by trial sponsors to:

- Improve access to patient populations that are challenging to recruit within the U.S. (e.g., racial and ethnic minorities, rare disease groups),
- Access samples of patients unfamiliar to specific elements of treatments or health services within U.S. health services settings, and
- Navigate practical and ethical limitations and challenges in RCTs.[36]

Amid these opportunities, fully leveraging ex-U.S. RWD to assess real-world efficacy in patient subgroups also faces challenges. Countries vary in terms of providing access to care, having and following clinical practice standards, and demographic heterogeneity, which are

a few factors among potentially many. These factors also may drive geographic differences in acceptable standards and thresholds for demonstrable medical product safety and/or efficacy and post-approval evidentiary standards and/or commitments for patient subgroups.

A growing focus[37] on improving clinical trial diversity in the U.S. suggests that ex-U.S. RWD to supplement or augment clinical trial diversity may be a useful strategy in coming years. Although the social dynamics and complexities that exist daily among diverse populations are not unique to the U.S., these dynamics are often viewed as factors that can severely limit clinical trial recruitment and completion as well as the generalizability of clinical trial results. For these reasons, ex-U.S. RWD is seen as one potential strategy to match and compare outcomes for specific racial or ethnic subgroups that are represented both within and outside of the U.S., especially if studies can control for observable sociocultural and social phenomena across distinct subgroups. Relatedly, ex-U.S. RWD can be used to supplement any dearth of U.S. RWD and clinical trial data about a specific racial or ethnic subgroup.

For example, despite decades of research identifying race and ethnicity as a risk factor for type 2 diabetes (T2D) and cardiovascular disease (CVD), Chinese Americans are historically underrepresented in U.S. cardiovascular outcome trials (CVOTs). To address this issue, Cai and Ji (2021)[38] compared patient data (e.g., blood glucose, blood pressure, and blood lipid levels) from Chinese-American individuals that were enrolled or met inclusion criteria to receive four glucagon like peptide-1 receptor antagonist (GLP-1 RAs) CVOTs (EXSCEL, LEADER, REWIND and SUSTAIN-6) treatments to a nationally representative sample of T2D patients in China (n= 25,411). The researchers descriptively compared key baseline characteristics of the populations in each trial and estimated the proportions of patients who would have met six key inclusion and exclusion criteria (age, HbA1c, BMI, eGFR, CVD history and antidiabetic medication) in each trial. Leveraging this data assisted with filling an important research gap of including Chinese Americans in cardiovascular studies and supported updated labeling guidelines for related medications.

Although demonstrable value exists in leveraging ex-U.S. RWD to supplement or augment U.S. clinical trial data, the value and utility of ex-U.S. RWD should be interpreted on a case-by-case basis. Most importantly, ex-U.S. data should not be used as a strategy to circumvent clinical trial outreach and engagement with underrepresented subgroups. Ex-U.S. RWD has demonstrated utility across a number of pertinent trial domains, such as meeting post marketing requirements (discussed in the "Using RWD to Supplement Clinical Trials for Subgroup Analysis" section). Several methodological considerations exist that warrant close examination prior to drawing conclusions about a given subgroup based on ex-U.S. RWD analysis.

Leveraging RWD to Address Shortcomings in Trial Data Concerning Racial/Ethnic Subgroups

Racial/Ethnic Subgroup Data Missingness and Misclassification

Data missingness within health systems refers to the absence of certain types of data. Data missingness can cause evidence gaps regarding the combined effects of race, ethnicity, ancestry, and genomics on health and treatment outcomes. Part of this missingness is due to how race and ethnicity data are neither systematically not accurately captured across U.S. health systems. In fact, an estimated 11 to 22 percent of hospital systems did not collect race and ethnicity data and an estimated 18 percent of cancer registries are missing race and ethnicity data.[39] Also, race and

ethnicity data were reported as missing in nearly 80 percent of cases of lab-confirmed COVID-19 from a large payor database, despite a clear racial disparity in the number of COVID-19 cases.[40]

Racial misclassification is also an issue as certain racial/ethnic groups are more likely to be misclassified, especially if genetic ancestry is not considered. This misclassification may impact causal inferences about treatment outcomes among demographic subgroups. For example, providers may erroneously code Hispanic/Latino/Latinx, Middle Eastern/North African, and Native American patients as 'white' or 'other'.[41] Also, in cases where structured EHR fields are used to collect race/ethnicity data, providers may inadvertently force patients to code themselves as belonging exclusively to one demographic group versus many for those who may identify as multiracial. In addition, in some cases like emergency treatment situations, race/ethnicity can sometimes be reported by others versus the patients themselves. Lastly, some patients may not trust health systems with their race and/or ethnicity data and may therefore decline to report it or report it inaccurately for this reason. All of these example scenarios can contribute to any observed lack of consistency in race/ethnicity data reporting across health care providers, which can interfere with or complicate data linkage efforts and common data modeling as well as general data availability, reporting, collection, curation, and integration.

Optimizing Racial/Ethnic Subgroup Data to Assess Real-World Efficacy

Race, ethnicity, ancestry, and genomic data are important to assess in health care and research, as complex interplays among a person's biology, environment, and environmental/social interactions can affect a person's overall health, disease status and/or risk, and responses to drugs, medical products, and devices. Yet, data indicating these factors are often missing and/or not considered in everyday health care scenarios, even when it is arguably necessary and actionable to do so for high-risk patient subgroups.

What results are limitations to real-world assessments of medical product and care utilization, treatment outcomes, intervention impacts on quality of life, and barriers to more efficient and targeted patient recruitment for clinical trials assessing real-world efficacy in patient subgroups.

RCT phases II and III involve assessments of treatment dosage, efficacy, and safety within a specific cohort of patients that meet very specific inclusion and exclusion criteria, lending to comparatively greater internal validity among the cohort than external validity to the general population.[42] If during these phases a clinical trial cohort largely represents a single racial/ethnic subgroup, and if the study assumes that confounding factors are uniformly distributed across all racial/ethnic groups within the dataset by virtue of the randomization process, then the study is inherently biased due to an overestimated treatment effect size for the overrepresented racial/ethnic subgroup Often, participants that are recruited and chosen for inclusion in phases II and II in RCTs identify as one race over another, regardless of ancestry, for reasons that have been empirically explored in recent years (e.g., physician bias, unclear or ambiguous inclusion/exclusion criteria, racial/ethnic population density, etc.).[43] Thus, researchers and trial sponsors may turn to RWD/E generated during RCT phase IV (post-market phase) to address this missing data and hopefully, determine whether real-world efficacy or treatment effects might differ significantly between racial/ethnic subgroups that were over-represented versus underrepresented/unrepresented in RCT phases II and III.

Leveraging RWD to Address Shortcomings in Trial Data Concerning Pregnant and Lactating Persons and Sexual/Gender Minorities

Pregnant and Lactating Persons

Pregnant and lactating persons are often excluded from or are otherwise unengaged in clinical trials and are classified as vulnerable populations under the U.S. Common Rule.[44] This exclusion has contributed to a dearth of evidence on drug safety and efficacy during pregnancy and lactation for both pregnant and lactating persons and their fetuses and nursing children. Annually in the U.S., approximately four million pregnant people give birth and 70 percent of this population take at least one prescription medication during their pregnancy.[45] Several initiatives are underway to address evidence gaps among this subgroup, including recommendations and an implementation plan from the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC).[46]

RWE studies to assess treatment safety and efficacy in pregnant and lactating persons can be a key strategy to address shortcomings in clinical trials that may fail to assess medical product safety and efficacy in this population.

RWE studies to assess treatment safety and efficacy in pregnant and lactating persons can be a key strategy to address shortcomings in clinical trials that may fail to assess medical product safety and efficacy in this population. In addition, these studies also may complement pre-approval clinical trial data and importantly, address the overall dearth of product safety and efficacy evidence that exists about this population. Given that prospective and retrospective registry studies[47] are most often used to observe and assess real-world safety and efficacy in pregnant and lactating persons, these sources can be used to augment existing clinical trial data, which may be more compelling to medical product regulators.

Sexual/Gender Minorities

RWD stratified by sex, gender, gender identity, and sexual orientation are important to determine and measure observable differences in treatment effects among these subgroups that could be due to hormonal exposure and influence, body mass index, and other biological or non-biological factors.[48] However, data collection practices across health systems tend to vary in terms of reporting patient sex, gender, gender identity, and sexual orientation, rendering RWD collected in health system settings inconsistent and potentially unreliable for this form of subgroup analysis. Imprecise health data collection can lead to mismeasurement of patient characteristics (e.g., when gender identity is reported as sex) or data misuse (e.g., provider assumptions that none of an individual's sex traits differ from their reported sex) leading to unwanted negative impacts for these individuals, and poor overall data quality.[49]

Ultimately, such differences in data collection and the lack of reliable data render it difficult for researchers to assess real-world efficacy among these particular patient subgroups, and to determine strategies to address health care disparities that exist among these subgroups in the real world.

The National Academies of Sciences, Engineering, and Medicine has developed guidelines to improve the consistent collection, measurement, and reporting of sex, gender, gender identity, and sexual orientation data. For example, the guidelines recommend that data collection efforts should not treat sex as a biological variable with gender or use these terms interchangeably. They further recommend that robust privacy and confidentiality standards must be maintained. Research findings should be shared[50] with respondents to ensure that individuals and their communities can benefit from sharing data.

Equitable Strategies and Best Practices to Address Subgroup Data Missingness

Missing data not only leads to underpowered and biased results, but is also a health data equity issue that may negatively affect minority patient access to novel treatments and care. Data equity is defined as the need for high-quality, disaggregated racial/ethnic data to capture inequities and underlying social factors associated with health needed to develop evidence-based solutions that inform public policies.[51]

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Several best practices may be considered when leveraging RWD/E to address subgroup data missingness (see **Figure 3**). First, RWD/E strategies should be incorporated into the study design process at earlier as opposed to later stages, such as during protocol development and through a missing data plan. Second, when and wherever possible researchers should be intentional about collecting data on and controlling for race, ethnicity, ancestry, genomics, sex, gender/gender identity, pregnant/lactating status, and social determinants of health, to name a few. These analyses should be planned a priori, powered for analysis, use well-defined categories, and maintain transparency in reporting. Researchers also should consider equity at the onset of creating datasets and contemplate how the datasets would perform or be useful to capture and assess real-world phenomena on treatment effects.

Figure 3 Best Practices for Leveraging RWD/E to Address Subgroup Data Missingness

- Incorporate RWD/E strategies early in study design process
- Collect data on and controlling for race, ethnicity, ancestry, genomics, sex, gender/gender identity, pregnant/lactating status, and social determinants of health
- Use categorical terminology consistently and appropriately
- Create distinct subgroup definitions applicable across the globe
- Integrate collection of race and/or ethnicity data process into the delivery of health care
- Address regulations in local jurisdictions that impact data collection
- Support data quality with information technology infrastructure
- Mitigate against unanticipated consequences of collection
- Identify and track classification variability
- Involve patients in the study development of the process
- Communicate how and why data will be used and reporting back to communities

Leveraging RWD to Improve Care Among Patient Subgroups

Improving Underrepresented Patient Subgroup Access to Clinical Trials

As a strategy to improve underrepresented patient subgroup access to biomedical innovations in health care, researchers are innovating around and undertaking strategies to recruit and engage demographically and biologically diverse patient subgroups in point-of-care (POC) trials[52] that can improve generalizability in trial results. As an operational approach to pragmatic trials, and potentially a faster method compared to RCTs,[53] POC trials can bridge evidence gaps that exist between research, practice, and health policy. Bridging this gap with policy, in particular, is critical to ensure that patient subgroups are appropriately served by the clinical research enterprise. Importantly, POC trials that involve randomization minimizes concern about potential confounders that may be observed among and across patient subgroups.

POC trials can bridge evidence gaps that exist between research, practice, and health policy.

Significant work and progress are needed, however, to ensure POC trials are conducted routinely. By involving and engaging health system stakeholders with the greatest needs and vulnerabilities, including but not limited to patient advocacy organizations and patients from demographically underrepresented subgroups, and by simultaneously leveraging POC trial infrastructure, staff, and other resources, is the potential exists to achieve broader clinical trial diversity and strengthen the patient subgroup diagnosis and treatment process.

Building Capacity for Patient Subgroup-Derived RWD

Engaging underrepresented groups in clinical trials requires addressing current and historic barriers to participation (i.e., mistrust in the clinical research enterprise, inaccessible clinical trial sites) and cultivating and sustaining environments within communities that are built on mutual respect and trust in researcher-participant and patient-clinician relationships. Furthermore, addressing structural and navigational barriers to clinical trial participation (e.g., transportation, childcare, time off work, etc.) remains important, especially for communities residing in remote areas or areas that are not within reasonable and/or affordable proximity to clinical or POC trial sites. Lastly, given these challenges and others that accompany the process of sharing or returning blinded or unblinded study results to participants, researchers should determine and implement strategies with input from underrepresented communities that return multiple forms of value to research participants beyond return of results (e.g., groups learning more about their risk factors, monetary compensation for research participation, receiving genetic information that can inform larger family risk, etc.), randomized access to treatment, and monetary compensation.

Researchers, trial sponsors, and health systems also should leverage RWD/E to identify sites with high-population densities of patient subgroups that are both underrepresented in clinical trials and at high risk of disease misdiagnosis or untimely disease diagnosis. These subgroups should be closely considered for risk of potential exclusion due to treated or untreated comorbidities early in trial design phases. Also, whenever possible, researchers, trial sponsors, and health systems should offer members of those communities the opportunity to give feedback on the trial/study

design, data that is to be collected/ generated, and the research question. This particular form of engagement can help research teams build trust and share power with members of those communities, help members of patient subgroups ultimately determine whether or not participation would be meaningful and/ or feasible to/for them, and help patients build stronger confidence in their treatment decisions.

For example, to help highlight racial/ethnic disparities in transthyretin (TTR) amyloidosis diagnosis, treatment, and access to clinical trials for novel treatments, the Amyloidosis Research Consortium (ARC) has highlighted the experiences and diagnostic odysseys of ATTR amyloidosis patients of African and non-African descent.[54] Despite the high burden of TTR cardiomyopathy among patients of African descent, and despite the fact that this patient subgroup carries the greatest cardiovascular disease burden in the U.S.,[55] clinical sites in geographic regions serving patients of largely African descent and/or Hispanic patients have rarely been sites for TTR amyloidosis clinical trials.[56] To help empower patients and health systems with diverse patient-derived RWD, ARC is collaborating with TTR amyloidosis care providers and patients across several communities to develop and validate an amyloidosis disease specific, patient-reported outcomes tool called the "ATTR-QOL." According to ARC, this tool will "provide the research field with a single, standardized questionnaire that eliminates gaps in measurement and is appropriate for use for any ATTR subtype or symptomatology."[57]

Conclusion

In summary, challenges and opportunities exist to leverage RWD to observe and measure real-world efficacy in patient subgroups. The lack of global, standardized racial/ethnic categories, along with different cultural and social perspectives in norms around categorizing such data, makes collecting and analyzing race and/or ethnicity data difficult. The concept of race as a social construct adds to the difficulty of collecting race and/or ethnicity, as racial categories might look different in other countries. The origin of race data is often unclear and may conflate behavioral/environmental risk factors with genetic/risk factors. A lack of consensus on a set of diversity variables often exists; researchers are unsure which variables to use to define and bring out variability. The lack of agreement on regulatory applications for ex-U.S. data in U.S. subpopulations can create challenges, in addition to difficulty in accessing RWD/E in underdeveloped countries.

However, these challenges do not undermine the benefits of leveraging ex-U.S. RWD to supplement U.S. collected clinical trial data. The lack of global racial/ethnic standardized categories; variability in race/ethnicity and sex, gender, gender identity, and sexual orientation data collection methods; and the difficulty in accessing RWD/E in underdeveloped countries all serve as barriers to engaging underrepresented groups in clinical trials, specifically groups in different countries. By considering each of these unique characteristics among patients and treatment options available to them in the real world, clinicians can make more informed decisions and provide more personalized care.

Policy plays a crucial role in ensuring that patient subgroups are appropriately served by clinical research. Therefore, polices that are related to the research and development of treatments that prioritize the equitable inclusion of patient subgroups, which have previously been underrepresented in clinical research, are essential in order to ensure that medical advances are informed by all people who may need them.

Appendix A: Real-World Efficacy – Patient Subgroups Workstream Members

The workstream comprised of representatives of member organizations of the 2022 Duke-Margolis Real-World Evidence Collaborative's Real-World Efficacy – Patient Subgroups workstream. We thank the members listed below for informing the development of this paper.

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Appendix B: 2022 Real-World Evidence Collaborative Advisory Group

This paper also was informed by the expert collaborators in the 2022 Duke-Margolis Real-World Evidence Collaborative Advisory Group. We thank the members of the Advisory Group, for informing the development of this paper. The following list reflects the 2022 Advisory Group roster, which advised on the initial development of this work stream.

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Appendix C: Participants at the December 13-14, 2022 Workshop on Real-World Efficacy Patient Subgroupsp

This paper also was informed by participants in the 2022 RWE Collaborative's December 13-14, 2022 Workshop on Real-World Efficacy Patient Subgroups. We thank the participants listed below, whose presentations and perspectives informed the development of this paper.

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Appendix D: Literature Review

This literature review served as the initial examination of real-world data and patient subgroups. From this literature review, we determined the importance of ex-US RWD in real-world efficacy and patient subgroups; 14 of the 16 suitable studies found were conducted outside the United States.

Author/ Study (Year)	Subgroup of Analysis	Real-World Data Source	Real-World Data Extraction Method	Subgroup Analytical/ Statistical Method	Key Findings: Conclusions
Tseng et al., 2017	Patients with left ventricular systolic dysfunction (LVSD). N=287	Results from retrospective cohort study of patients with LVSD at the Mayo Clinic in Rochester, Minnesota. Longitudinal health information was extracted from clinical data stored in the Mayo Clinic database.	Data extracted from EMRs.	Incidence of safety and efficacy outcomes in cohort was compared to that of the subgroup of patients with LVSD (defined as left ventricular ejection fraction ≤40%) and/or clinically diagnosed HF in the RE-LY, ROCKET-AF, and ARISTOTLE trials.	Findings are consistent with the results of previous trials and adds to evidence that that DOACs can be safely used for stroke and systemic embolism prevention in patients with LVSD.
Huang et al., 2018	MSM and transgender women Meta-analysis and systematic review, N is unspecified	Six RCTs (4 real-world) and 8 open label extension studies included.	Data extracted from the screened literature.	Narrative review used for previous RCTs and OLEs to avoid calculating results based on the same sample. Combined event rate and random-effects meta-analysis to estimate the incidence of HIV and of serious AEs.	PrEP "significantly reduced HIV incidence... indicating the utility ot this biomedical HIV prevention intervention in curving HIV transmission among MSM."
Oksi et al., 2019	C. Diff patients using bezlotoxumab. N=46	Retrospective cohort using medical records evaluating efficacy and safety of BEZ in an intent-to-treat setting in all (five) university hospitals in Finland. From patient records, collected data on background diseases, immunosuppression, past CDIs, and severity (based on Zar score) of the last CDI before the treatment with BEZ.	Data extracted from EMRs.	Specific methods unspecefied.	Real-world experience on BEZ efficacy seems to be promising. success with BEZ together with SOC in preventing rCDI may be rated as high. Among a subgroup of our patients, those already evaluated to be in need of FMT, BEZ seems to be an alternative option.
Shin et al., 2020	Korean patients with hypertension. N=3011	Results from open, noncomparative, noncontrolled, prospective, single-arm, multicenter, observational study to study efficacy and safety of nebivolol.	Data from an observational study conducted by investigators.	Subgroup analysis: the primary efficacy in subpopulations of patients who were newly diagnosed with essential hypertension at study entry (de novo); taking other monotherapy antihypertensive at study entry who switched to nebivolol during the study (monotherapy switch); taking one or two other antihypertensives [including CCBs, RAS blockers (ARBs or ACEIs) and diuretics] at study entry who received add-on nebivolol during the study (add-on therapy).	Real-world study in Asian patients with essential hypertension with and without comorbidities, demonstrated the efficacy and safety of once daily nebivolol, either as monotherapy or add-on therapy.
Laroche, Nkrumah, & Ng 2020	Black and Afro-Latinx patients with glaucoma. N=76	Results from retrospective noncomparative single-center study of 76 Black and Afro-Latinx patients with glaucoma who underwent phacoemulsification cataract surgery and Hydrus microstent placement for treatment of glaucoma at single practice.	Data from observational study conducted by investigators.	Subgroup analysis: Patients were stratified into mild, moderate, or advance glaucoma according to the Hodapp–Parrish–Anderson criteria.	Study demonstrated the efficacy of phacoemulsification cataract surgery and Hydrus microstent in reducing the medication burden while maintaining lower IOP in Black and Afro-Latinx patients with glaucoma.

Author/ Study (Year) *continued*	Subgroup of Analysis *continued*	Real-World Data Source *continued*	Real-World Data Extraction Method *continued*	Subgroup Analytical/ Statistical Method *continued*	Key Findings: Conclusions *continued*
Morton et al., 2020	Patient subgroups are not specifically discussed, as the guidelines for photodynamic therapy are organized by pathology type alone.	References observational or retrospective studies but does not provide details about their data source.	References observational or retrospective studies but does not provide details about their extraction method.	References observational or retrospective studies but does not provide details about subgroups or analytical methods.	Studies incorporating RWD/RWE are used by to supplement these dermatological guidelines.
Tambo et al., 2020	Japanese patients with histologically diagnosed advanced or recurrent NSCLC and a PD-L1 tumor proportion score >= 50% receiving pembrolizumab as first-line tx. N=95	95 patients enrolled in this multicenter retrospective study from February 2017 to December 2018.	Clinical data collected from EMRs. Assessed objective response rate, progression-free survival, OS, and immune-related AEs .	Collected data included: age, sex, smoking status, ECOG-PS, stage, histology, history of palliative radiotherapy, and metastatic site. OS and PFS evaluated using Kaplan-Meier method and differences between patient groups for each factor compared by log-rank test. Cox regression used to calculate hazard ratio for each. Multivariate analysis used to detect independent prognostic factors.	ORR and PFS was 40% and 6.1 months, respectively. OS did not reach median. PFS lower than in clinical trials. Non-adenocarcinoma and a large number of metastatic sites correlated with poor PFS and OS; PFS and OS shorter in patients with interstitial lung disease; gender, age, smoking status, etc., all were not found to be correlated with OS in pembrolizumab-tx pts with advanced NSCLC.
Sciarra et al., 2021	Age (in relation to efficacy and safety of atrial fibrillation ablation). N=2534	ClinicalService: a national cardiovascular data repository and medical care project designed to describe and improve the quality of diagnostic and therapeutic strategies using technologies and therapies in the Italian clinical practice. Each patient included in the ClinicalService project provided informed consent for the data collection and analysis.	Data extracted from ClinicalService on study endpoints: procedural times, procedure-related complications, and AF recurrences.	Subgroup analyisis: the efficacy and safety outcomes in patients <41 years (defined as "very young" patients group) and in patients >74 (defined as "very old" patients group).	Data demonstrated a high degree of safety during CBA across all patient ages. Procedural performance and complications were similar between different ages.
Ghosh et al., 2021	Type 2 diabetes patients in India. N=430	Results from structured proforma to collect information from pre-existing hospital records of the participating doctors. Data collected were anonymized and information collected included demographic data, antidiabetic medications, and glycemic status of the patient at the time of initiation and after 3 months of teneligliptin therapy.	Health Record extraction.	The glycemic efficacy was assessed by analyzing the mean change in values of glycosylated hemoglobin (HbA1c), FPG, and PPG from baseline following teneligliptin therapy.	teneligliptin significantly improves glycemic parameters in Indian T2DM patients when prescribed as monotherapy or as add-on to one or more antidiabetic drugs.

Author/ Study (Year) *continued*	Subgroup of Analysis *continued*	Real-World Data Source *continued*	Real-World Data Extraction Method *continued*	Subgroup Analytical/ Statistical Method *continued*	Key Findings: Conclusions *continued*
Fitton et al., 2021	Rheumatoid arthritis patients. N=115	Used prospective database for all patients with RA treated with a JAKi and retrospective data were collected from clinical notes and electronic health records. DAS28-CRP scores and components recorded at baseline, 3 and 6 months.	Data extracted from EMRs.	Patient demographics and clinical characteristics were summarized for each group using proportions of patients, median with interquartile range (IQR) or mean with standard deviation as appropriate. Mean changes in DAS28-CRP score from baseline were calculated at 3 and 6 months and reported for the combined cohort and individual treatment groups. Subanalyses according to number of prior bDMARD failures were performed. All patients had baseline DAS28 scores and components recorded.	Clearly observed clinical improvement in patients treated with JAK inhibition following MTX-inadequate response and in the most bDMARD-refractory of patients.
Chinushi et al., 2021	Japanese patients with ventricular tachycardia. N=41	Retrospective cohort study of 41 patients included in the Nippon-storm study database.	Data collected from Nippon-storm study database. The study evaluated outcomes of anti-tachycardia pacing devices in real-world settings.	The study divides its subjects into 3 subgroups based on heartrate and ventricular tachycardia. The three subgroups are: greater than or equal to 50% success rate for both fast (188bpm+) and non-fast (120-187 bpm) VT (both useful), greater than or equal to 50% success rate only for non-fast VT (non-fast VT useful), or greater than or equal to 50% success for neither (neither useful). Those with greater than 2 episodes of ATP were included as an additional subgroup.	Patient-by-patient basis ATP programming is useful for both non-fast and fast VT in 78% of Japanese patients with structural heart disease. Neither ischemic nor non-ischemic structural heart disease associated with efficacy of ATP device treatment.
Hung et al., 2022	Asian patients with Recurrent Epithelial Ovarian Cancer using Bevacizumab. N=67	Retrospective cohort study using data from a tertiary medical center in central Taiwan. Patients who had EOC with first relapse between 2011 and 2019 were enrolled. Patients' medical histories, medication treatment, and relevant information were collected. The outcomes were PFS and overall survival (OS).	Data extracted from EMRs.	Differences in baseline characteristics between the two treatment groups were compared using the Mann–Whitney U test and chi-square test for continuous and categorical variables, respectively. The Kaplan–Meier method was used to generate survival curves for OS and PFS. Cox proportional hazard analysis was performed to determine the association of bevacizumab treatment with OS and PFS after adjustment for relevant variables. Subgroup analysis was conducted to determine if a significant variation was present in the aforementioned association.	Treatment with bevacizumab in addition to commonly used chemotherapy significantly prolonged the progression free survival of Asian patients with recurrent EOC in the real-world setting.
Qiu et al., 2022	Chinese ALK-rearrangement NSCLC patients with Brain Metastases. N=57	Retrospective cohort study of 57 patients treated across 7 hospitals in Sichuan, China from October 2018 to May 2020.	Data extracted from EMRs: gender, age, ECOG performance status score, smoking history, pathological type, TNM stage, metastasis site, gene status). Efficacy and AE data collected through EMRs and phone calls.	A chi-square test or Fisher's exact test was used to compare the objective response rate and disease control rate between patient subgroups (gender, age, smoking history, prior chemotherapy, prior brain radiotherapy, etc.). Kaplan-Meier method used to estimate survival probabilities. Normal approximation method used to compare the estimated 6-and 12-month event-free probabilities between patient subgroups.	No difference found in intracranial ORR and DCR across subgroups. For whole body efficacy rates, patients with prior brain radiotherapy had slightly higher event-free probabilities.

Author/ Study (Year) *continued*	Subgroup of Analysis *continued*	Real-World Data Source *continued*	Real-World Data Extraction Method *continued*	Subgroup Analytical/ Statistical Method *continued*	Key Findings: Conclusions *continued*
Ortega-Franca et al., 2022	Pre-treated Non-Small-Cell Lung Cancer PD-L1 positive patients. N=113	Retrospective study.	EMR extraction.	Lung Immune Prognostic Index (LIPI) used to assign patients to 3 prognostic subgroups based on derived neutrophil to lymphocyte ratio and LDH in blood. Prognostic impact of LIPI on progression-free survival and overall survival evaluated with Cox method. Combined effect of LIPI and other prognostic factors evaluated with multivariate regression.	Patients with intermediate and poor LIPI had worse PFS versus good LIPI, and statistically significant worse OS. Patients with both good-LIPI and high (>= 50%) PD-L1 had better OS than all other subgroups defined by LIPI and PD-L1.
Zhang et al., 2022	Chinese patients with relapsed/ refractory mantle cell lymphoma. N=121	Data from 121 adult R/R MCL patients initiated on ibrutinib monotherapy or ibrutinib-based combination therapy between August 2017 and December 2020 were included.	Data came from 13 medical centers in China. The article does not specify whether obtained in an EMR or not.	Subgroup evaluation: age, gender, ECOG-PS (Eastern Cooperative Oncology Group Performance Status), Ann Arbor stage, refractory disease, number of previous therapy lines, histology of subtype, Ki67, simplified MIPI, MIPI-c, Bulky mass size, number of extranodal involvements. Chi-square, Fisher exact, or Wilcox rank-sum tests used to compare between two tx groups. All time-to-event endpoints estimated using Kaplan-Meier survival method.	Results showed positive results for mono-or-combination therapy, though the effect for combination therapy was greater. Subgroup analysis showed differential effects: males with a Ki67<30% with 1 previous line of therapy of the non-blastoid subtype with less than 2 extranodal sites involved benefited most from combination therapy. Though this is very specific, it is a promising example of RWD/E supporting individualized therapy.
Thaler et al., 2022	Israeli patients with advanced Parkinson's Disease. N=161	161 Device-aided therapy patients included in this retrospective study.	Data extracted from the Israeli Maccabi Health Services: a "cradle-to-grave" database EMRs of 2.5M active members (~25% Israel population). Collects data from prescriptions, MHS pharmacy network purchases, MHS central lab, consultations, hospitalizations, and procedures.	Study does not particularly focus on patient subgroups in terms of their characteristics, but rather defines 3 subgroups based on different therapeutic regimens. In addition to evaluating the efficacy of the three regimens, the authors also tracked associated health care visits and costs.	DAT effective and well maintained in these patients. LCIG (levodopa-carbidopa intestinal gel) may have best persistence rates out of the three regimens.

Appendix E: Glossary

Subgroup: Describes an analysis of a subset of participants (e.g., selected set of individuals with specific patient characteristics within an individual study or across studies in the case of individual patient data meta-analyses).[7]

Subpopulation: "Describes a specific group of individuals with common patient characteristics (e.g., race and/or ethnicity, age, risk factors) that is the target of an intervention or a policy recommendation.[7]

Efficacy: Measured in an explanatory trial and it is how well an intervention works in ideal/controlled circumstances. In Efficacy studies, the population is highly selected, homogenous and there are several exclusion criteria. The providers are highly experienced and trained the intervention is strictly enforced and standardized.[4, 5]

Effectiveness Assessed in pragmatic trials and it is how well an intervention works under real-world circumstances. In effectiveness studies, the study population is heterogenous with few to no exclusion criteria. The providers are representative usual providers and the intervention is applied with flexibility. Concurrent interventions and cross over are permitted.[58]

Real-world efficacy: Efficacy of a particular treatment in real-world settings, rather than to the controlled conditions of a clinical trial.

Patient subgroup: A disaggregated group of patients with shared characteristics, such as age, gender, race and/or ethnicity, comorbidities, and single or multiple gene variations.

Pragmatic: Describes trials that help users choose between options for care and seeks to answer the question, "Does this intervention work under usual conditions? [59]

Explanatory: Describes trials that test causal research hypotheses and seeks to answer the question, "Can this intervention work under ideal conditions?"[60]

Estimand: A statistical quantity to be estimated that provides a precise description of the treatment effect reflecting the research question.[17]

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