

# Understanding How RWE Can Affect the Management of Myeloma

A Q&A With Robert M. Rifkin, MD, FACP



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**The American Journal of Managed Care® (AJMC®):** From your perspective, how can real-world evidence (RWE) be used to gain insight into the field of myeloma?

**RIFKIN:** Over the years, we've collected a large amount of data in multiple myeloma research registries, which is often the foundation for some of the RWE in myeloma. What we've found is that approximately 40% of a representative sample of [patients with] myeloma were actually not eligible for clinical trials to advance the field. The reason they weren't eligible was largely that the inclusion and exclusion criteria of the trials were too narrowly focused. With very specific questions in mind, we had actually excluded a significant number of real-world [patients with] myeloma. In addition, RWE also helps us to work with various manufacturers and various stakeholders of new myeloma therapies to help them understand perhaps where their therapy might fit in the patient's myeloma journey.

**AJMC®:** Can you describe how RWE can contribute to future studies in the myeloma space?

**RIFKIN:** As we move forward, RWE will help us design more appropriate and more user-friendly, for lack of a better word, clinical trials. In medical oncology only 3% or so of our patients enter research trials; as things get more and more specific with targeted therapy, that percentage might become less. So RWE actually helps us explore potential study populations. When we bring a new myeloma therapy online, RWE will have helped us survey the landscape and can hopefully identify a clinical trial that will accrue rapidly and be relevant.

Initially people really didn't value RWE, but there has been a change in the mind-set of the FDA and other regulatory agencies so that you can now use RWE as a foundation for designing clinical trials. And I think that's really advancing the field. This will enable clinical trial designs to be much more applicable to a generalizable population with multiple myeloma. In addition, we're also actively involved in developing synthetic controls, which is a control population from within our evidence database, almost like a simulation to use RWE and help us design relevant clinical trials.

**AJMC®:** What characteristics of RWE studies can increase their quality and credibility?

**RIFKIN:** A lot of real-world studies, at least in my experience, take several forms. Initially, before you can do any of these, you have to do a feasibility study so you can see whether, for example, in my network, there are enough people with multiple myeloma. After you perform that basic assessment, you have to conduct an evaluation to see what's available in the electronic health record because those are data points that are relatively easy to extract. Probably the most important step at the end of the day, once you've done all that, is to validate what you're doing. Our group will then go in and do very careful chart reviews. We're now starting to look at ways to automate the chart review

process with artificial intelligence and natural language processing. This exercise allows examination of the data set for its robustness.

In short, demonstration of feasibility of eligible patients with myeloma in the network or the group you're going to study creates the foundation and must ensure that all of the study population have electronic health records. Within our group, we give careful consideration to the methodology of how to conduct the study properly and efficiently to get out of it answers to the questions at hand in a credible and nonbiased way.

**AJMC®: How can RWE contribute to the treatment decisions made by clinicians for the population with relapsed/refractory multiple myeloma?**

**RIFKIN:** The vast majority of decisions in the relapsed/refractory population are being dictated by clinical practice guideline and adherence to clinical pathways. It's not likely you can immediately take RWE and generalize it to how you're treating your patients. In the setting of relapsed/refractory myeloma, we tend to, as in most of oncology and hematology, employ evidence-based decision-making. So within our network, we follow the [National Comprehensive Cancer Network] guidelines. There is also an additional layer, which is the value in terms of economic impact and cost of care. So if, for example, you have 2 treatments that are equally effective but one is half the cost of the other, you would most likely pick the less expensive one. At some point, I do see RWE being integrated into clinical trial design and into the pathways, but that's quite a ways away.

**AJMC®: Is there a need for education regarding how RWE could be used in informing decisions?**

**RIFKIN:** Overall both providers and patients are vastly undereducated about RWE. A lot of folks probably don't fully understand what we do to accumulate it to create the projects and the studies. Hopefully, we can push things forward into the clinic as we design research trials to improve patient access and decrease cost.

In general, there is still a lot of education to be done in medicine. And there's probably even more education that needs to be done in terms of RWE and how it plays into medical oncology and hematology decision-making. Overall, there's a huge lack of education regarding what you can reasonably expect for conclusions from a real-world study and how to apply that into trial design and into

practice. Stakeholder education and understanding how to interpret the published literature is vital to the integration of RWE into clinical practice.

**AJMC®: What role does data adjustment play in the analysis of real-world data?**

**RIFKIN:** One of the things that we commonly deal with in RWE is missing data points or disparities among the group under study. And then, of course, everybody wants to adjust for this. Along the way, we need to have access to unadjusted data as a first step. At the time of publication, multiple statistical methods need to be reviewed and validated to be sure they're appropriate and that you make appropriate adjustments. You can keep performing statistical adjustments forever, if you will, to get what you need, and that's the wrong approach. There really needs to be a balance, but I think you'll never see a study published that's completely "unadjusted."

**AJMC®: Which study end points do you think are most relevant from an RWE standpoint, and are there some additional alternative end points that could be used for RWE studies?**

**RIFKIN:** In the past, in myeloma trials, the "gold standard" has been overall survival. If you examine the myeloma landscape at present, we're doing so much better with all of our new therapies ([bispecific T-cell engager] molecules, [chimeric antigen receptor T cells], monoclonal antibodies, selective inhibitors of nuclear export proteins, and [histone deacetylases]) that overall survival is no longer realistic as an end point. So I think you need to not look entirely at overall survival, but we need to be looking at progression-free survival (PFS), and there's PFS1 and PFS2, which is the second PFS defined by statisticians.

Time to next treatment is really important because now we get people in plateau phases that are lasting for many months to years. A new entrant into the myeloma arena is detection of minimal residual disease (MRD) by next-generation sequencing of multiparameter flow cytometry. MRD is starting to be looked at as a surrogate end point [because] it's a lot faster to determine than waiting for an overall survival end point to mature, or even at PFS. We need to closely examine time to next treatment and what the PFS2 is, and how they integrate into the development of RWE. As a patient's myeloma journey proceeds, time between relapses tends to decrease, and the integration of RWE will soon make a significant clinical impact. ♦