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Potential title: Real-World Data as an Evidence Source in Nuclear Medicine

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Throughout the course of routine clinical practice, real-word data (RWD) is obtained from various sources including medical claims, product and disease registries, electronic health records (EHRs) as well as prospective observational study settings. Real-world evidence (RWE) is generated by analyzing RWD for specific research questions to describe patients, treatments and outcomes.[1] RWE use is becoming particularly relevant in oncology, as only a small percentage of adult cancer patients worldwide are enrolled in clinical trials while the number of therapeutic options and the segmentation of patient populations are rapidly increasing, leading to the explosive growth of research questions and evidence gaps.[2]

RWE holds the promise of expanding evidence generation into routine clinical care settings to address questions that cannot be answered with data from traditional clinical trials, for example those related to rare cohorts of patients or those for which there is no clinical equipoise to permit ethical randomization. In drug development, RWE can be used to inform clinical trial design and feasibility during clinical development, and to provide natural history and standard of care context for the study population of interest. Following drug approval, RWE can support regulators and HTA bodies by providing real-world information on safety, effectiveness, and cost-effectiveness in the context of postmarketing requirements.[3] Finally, RWE can enable precision medicine by understanding the adoption of new therapies and diagnostics and comparing the effectiveness of different therapies in targeted populations.[4]

While many RWE initiatives rely on costly manual data input or already structured information, the broad adoption of EHRs worldwide over the past decade represents a promising source of rich clinical data. Deriving meaningful and trustworthy insights from the data, however, requires standardized data processing, rigorous quality assurance, and application of sophisticated analytic approaches. Harmonizing structured data, such as diagnosis codes, medication administrations, and laboratory results, to a common data model enables the merging of data from different sources. Extracting information from unstructured documents, such as free-text clinical notes or radiology and biomarker reports, allows for collection of deeper, more nuanced data elements such as assessments of tumor burden and response. While advances in AI hold the promise for automated interpretation of such unstructured data, high-quality evidence generation currently still relies on trained human curators' ability to follow standardized policies and procedures to guarantee internal consistency of the evidence.[4,5]

In order for RWE to generate actionable insights, it must provide information on clinical outcomes. In oncology, this requires new approaches to capture tumor burden assessments that ought to be tested for reliability, e.g. to capture real-world progression and real-world response from unstructured EHR documents as an alternative to Response Evaluation Criteria in Solid Tumors (RECIST).[6] In addition, information on survival can be collected from a combination of mortality surveillance tools beyond information in the EHR, such as national databases.

If RWE is deemed appropriate for a relevant scenario, a specific data source must be determined as fit for purpose to answer the underlying research question. In order to determine whether a dataset is regulatory-grade, Miksad and Abernethy propose a checklist that defines attributes including quality, completeness, transparency, generalizability, timeliness, and scalability.[5] Based on a specific RWE source a study design should be developed to address these attributes, including an analysis of the data source and target population (e.g., geographic representation), statistical approaches such as propensity score methods to control for measured confounding, and a detailed statistical analysis plan.[7] Such careful and transparent design is critical in leveraging RWE for decision-making along the product life cycle. Ongoing research into transparent and standardized approaches for RWE analyses remains critical. Organizations such as the Duke-Margolis Center for Health Policy are developing important guidance for the application of RWE.[3] Franklin et. al propose a similar structured process in the case of using RWE for regulatory decision-making.[7]

Several recent examples demonstrate that EHR-derived RWE already has the ability to impact access to new treatments and hence clinical practice in specific settings:

- The U.S. FDA approved a supplemental new drug application (sNDA) for palbociclib (Ibrance) to expand the label to male patients with breast cancer. Palbociblib had previously been approved for use in women with metastatic breast cancer. RWE derived from EHRs and other sources were used in addition to past clinical trial data to evaluate effectiveness and safety for the label expansion to male patients.[8]
- The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA accepted RWE as part of a post-approval risk management plan for trastuzumab emtansine (Kadcyla). EHR-derived data were used to evaluate the safety of the product in metastatic breast cancer patients with low left ventricular ejection fraction prior to initiation of treatment, a patient group that was excluded from clinical studies.[9]

Potential Applications to Nuclear Medicine

These are encouraging examples of the use of RWE to describe and facilitate the availability of treatments for patients with rare clinical conditions or those excluded from clinical trials where lengthy and costly prospective clinical studies may not be feasible. RWE also has significant potential applications in understanding the value of diagnostic or therapeutic radiologic procedures. Nuclear medicine procedures that are in common use may lack extensive prospective clinical evidence before becoming available, resulting in a heterogeneous reimbursement landscape and medical decision making uncertainty. Collection and analysis of

routinely collected RWE regarding the use and performance of novel diagnostic or therapeutic radiology could potentially generate the evidence needed to further assess the value of nuclear medicine procedures in specific clinical contexts.

For example, diagnostic PET procedures are sometimes performed prior to (and often even without) reimbursement. Whereas FDG PET for melanoma is typically covered by insurance plans in the US, the lack of prospective clinical studies demonstrating survival benefit limits reimbursement in Germany. Analysis of RWE could potentially demonstrate whether or not there is added value for FDG PET by comparing patient groups managed with or without access to FDG PET. Another opportunity might be to understand the therapeutic effectiveness of nuclear medicine treatments such as 89Sr, 153Sm, and 131I that were not subject to large-scale prospective randomized trials. Collection and analysis of RWD may be able to support the effectiveness of these therapies. Of course, as in any observational study, appropriate analytic methodology is necessary to mitigate potential unmeasured confounders and biases.[10]

High-quality RWE from electronic health records is increasingly recognized as an opportunity to fill evidence gaps, especially for applications for which prospective clinical studies are infeasible or where the potential benefit of the diagnostic or therapeutic intervention is large, as suggested by the U.S. FDA RWE program.[11] Nuclear medicine technology, in both diagnostics and therapeutics, represents a remaining frontier that could benefit from new insights derived from real-world evidence.

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