Review

Utilization of Real-World Data to Facilitate Clinical Trials for Patients with Lymphoma

Dai Chihara 1,*, Brian P. Hobbs 2, Matthew J. Maurer 3 and Christopher R. Flowers 1

1 Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
2 Department of Population Health, University of Texas-Austin, Austin, TX 78712, USA
3 Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN 55905, USA
* Correspondence: dchihara@mdanderson.org

Abstract: The future directions in leveraging real-world evidence (RWE) and real-world data (RWD) in the field of lymphoma, as compared to traditional experimental clinical trials, are poised to significantly impact research methodologies, treatment strategies, and patient care. Current methods of clinical trials involve a well-controlled design and patient selection bias. Integrating RWE and RWD with experimental clinical trials offers a multifaceted approach to understanding lymphoma and enhancing patient outcomes. In this review, we discuss how RWE has helped shape lymphoma clinical trials, and we compare and evaluate evidence obtained from real-world lymphoma studies/databases with that obtained from clinical trials. We also discuss methods for utilizing surrogate endpoints to facilitate clinical trials and expedite drug development. RWE can be leveraged to bridge the gap between data obtained from clinical trial populations and the broader patient population encountered in clinical practice, by highlighting differences in outcomes and the need for effective treatment strategies across diverse patient groups.

Keywords: lymphoma; real-world evidence; clinical trial; data science

1. Introduction

Real-world data (RWD) are data related to patient health status and/or the delivery of health care routinely collected from a variety of sources, such as electronic health records (EHR), claims and billing data, product and disease registries, patient-generated data, and data gathered from other sources that can inform on health status, such as mobile devices. Real-world evidence (RWE) is derived from the analysis of RWD. The objective of an RWE study is to describe the health status, management, and outcomes of a patient population, which can be used in comparison to clinical trials that treat very selected patients [1].

Many studies have been conducted in the past utilizing large data sets, such as population-based cancer registry data from the Surveillance, Epidemiology, and End Results (SEER) Program [2,3] and the National Cancer Database in the US [4,5], geographically defined populations [6,7], or country disease registries [8,9] to describe the outcomes general populations of patients. However, the terms “RWD” or “RWE” are increasingly used to describe such studies following the 21st Century Cures Act (Cures Act). The Cures Act was signed in December 2016 to accelerate medical product development and bring innovations and advances to patients more efficiently and faster. Following the Cures Act, the Food and Drug Administration (FDA) created a framework titled “Framework for FDA’s Real-World Evidence Program” in December 2018 to describe how the FDA plans to evaluate the use of RWE in drug approvals and post-marketing studies [1]. The framework describes the potential uses of RWE, including supporting label expansions, satisfying post-approval study requirements, and supporting new indications or changing labels to reflect changes in the standard of care. The scope of RWD studies includes but is not limited to (1) generating the hypotheses for randomized controlled trials, (2) identifying...
drug development tools such as biomarkers, (3) identifying specific patient populations for enrichment or stratification for trials, (4) assessing trial feasibility by examining the impact of planned inclusion and exclusion criteria in the relevant population, and (5) informing prior probability distribution in Bayesian statistical models.

The randomized controlled trial (RCT) remains the gold standard to demonstrate the impact on the safety and efficacy of experimental treatment compared to the control arm in a specific patient population. However, performing an RCT is not always feasible or even ethical in certain circumstances and may delay drug development and limit delivering effective treatments to patients faster. There is a general acknowledgment that the current regulatory approval process does not fully meet rapidly evolving healthcare needs, thus inspiring the statement from the FDA for utilizing RWD/RWE.

Accelerated approvals from single-arm trials can potentially utilize historical controls and RWE, as a comparator, particularly in rare diseases. One example of this was the development of blinatumomab for patients with acute lymphoblastic leukemia [10]. Effectively, RWE derived from standard-of-care data offers great potential for trial design and execution, and supports regulatory decision-making in drug development [11]. However, generating evidence from RWD that meets the fundamental regulatory requirements has been challenging despite the mutual interest from the FDA and disease investigators. In August 2023, the FDA provided guidance for industry use of RWE studies for regulatory decision-making regarding drug and biological products [12]. The guidance addressed that for the FDA to consider RWE for regulatory purposes, RWE studies should be conducted meticulously similar to prospective clinical trials. Sponsors should engage with the FDA early in the process of designing the study, discussing if the planned sources of data are reliable and unbiased, and if the use of RWE is feasible and appropriate to address the specific clinical question. Sponsors should also submit the protocol and statistical analysis plan in addition to patient-level data. These are rigorous requirements, and therefore, the majority of RWE studies currently reported or conducted fall short of supporting regulatory decision-making. In this review, we summarize pivotal RWE studies on diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), and discuss future directions of RWE studies related to these lymphomas.

2. Real-World Data in Lymphoma
2.1. Diffuse Large B-Cell Lymphoma

RWE studies have been conducted in DLBCL to describe high-risk patient populations and outcomes from specific treatments, such as chimeric antigen receptor (CAR) T-cell therapy [13,14]. The SCHOLAR-1 study was an international pooled investigation of patient-level data from four data sources: two large phase 3 clinical trials (the Lymphoma Academic Research Organization-CORAL and the Canadian Cancer Trials Group LY.12) and two observational cohort studies (the MD Anderson Cancer Center and the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence). It evaluated the responses and overall survival (OS) rates in patients with refractory large B-cell lymphomas (which included transformed FL and primary mediastinal B-cell lymphoma) [15]. The main objective of the study was to describe the outcomes of patients with refractory DLBCL whose disease failed to respond to immunochemotherapy and to establish the reference of response and survival outcomes for future trials targeting the same patient population. Refractory DLBCL was defined as progressive disease (PD) or stable disease (SD) as the best response to chemotherapy, or relapse ≤ 12 months after autologous stem cell transplant (ASCT). Among the 861 patients whose records were summarized, 636 patients had refractory disease. The overall response rate (ORR) to the second- or later-line of therapy was 26% and the median OS was 6.3 months. Of note, the complete response (CR) rate from second-line treatment was only 3% in patients who were refractory to first-line treatment. Long-term survival was rare and 20% of patients were alive at 2 years.

This SCHOLAR-1 study described a high-risk patient population with an urgent unmet need for novel effective treatments, and effectively served as a “historical control”
to contextualize the impact of axicabtagene ciloleucel (axi-cel) evaluated in a single-arm phase 2 trial called ZUMA-1 [16]. In ZUMA-1, the ORR and CR rates were 82% and 42%, respectively, and 40% of patients demonstrated CR at a median follow-up of 15.4 months. Based on the results of the ZUMA-1 trial, the FDA granted an accelerated approval of axi-cel in patients with DLBCL after ≥2 lines of treatment (3L+). The data from SCHOLAR-1 were available for review by the FDA as a historical control at the time of the new drug application (NDA). A follow-up analysis comparing the patient's outcomes between ZUMA-1 vs. SCHOLAR-1, using a propensity score (PS) matched patient cohort, further supported the superiority of CAR T-cell therapy over the standard of care in this high-risk patient population [17]. The ORR and CR rates were 83% and 54% in ZUMA-1 vs. 34% and 12% in SCHOLAR-1, respectively. The 2-year OS was 54% in ZUMA-1 and 20% in SCHOLAR-1, and the study reported a 73% reduction in the risk of death. Trials such as ZUMA-7 were conducted based on studies reporting the impact of CAR T-cell therapy, and the indication of CAR T-cell therapy has been expanding [18].

Other analyses have allowed indirect comparisons between outcomes in pivotal single-arm phase 2 trials and RWE from retrospective studies. For instance, the L-MIND trial enrolled 81 patients with DLBCL who relapsed or had refractory disease (defined as progression within less than 6 months from the completion of first-line therapy, or showing less than a partial response [PR]) after previous treatments with one to three systemic regimens. Patients received tafasitamab and lenalidomide (25 mg/day; 3 weeks on, 1 week off) for up to 12 cycles, followed by tafasitamab maintenance until disease progression. The primary endpoint of the study was the best ORR. A total of 50% of patients received tafa-len as a 2L treatment, 43% as a 3rd line (3L) treatment, and 19% of patients had primary refractory disease. The ORR was 60% with 43% of patients achieving CR [19]. Based on the results, tafa-len was approved by the FDA in July 2020. A 5-year follow-up of the L-MIND study confirmed the long-term efficacy of this treatment in responders with a median duration of response not reached [20].

Several comparative effectiveness studies using RWD were conducted around the time tafa-len was approved. First, the retrospective RE-MIND study was conducted to delineate the contribution of tafasitamab added to lenalidomide [21]. Data from patients with relapsed DLBCL who received lenalidomide monotherapy were collected using EHR data abstraction from 42 participating centers. Of the data collected for 490 patients, 140 patients met the inclusion criteria of the L-MIND study, received a lenalidomide starting dose of 25 mg, and fulfilled the 6-month follow-up criteria. After the selection, 76 patients were matched (1:1) to patients in the L-MIND study using estimated PS from nine pre-specified baseline covariates. The RE-MIND study showed that the combination therapy almost doubled the ORR (67.1% vs. 34.2%), and the duration of response was significantly longer (20.5 months vs. 6.6 months) compared to lenalidomide monotherapy.

The RE-MIND2 study compared the effectiveness of tafa-len to other standard regimens of interest for relapsed/refractory DLBCL, including ones in the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) [22,23]. For RE-MIND2, data from 3454 patients with relapsed/refractory DLBCL were collected using EHRs from 200 centers. Similar to the RE-MIND study, patients were matched to patients in the L-MIND study using six to nine clinical factors. In the RE-MIND2, tafa-len was associated with a significantly longer OS compared to bendamustine plus rituximab (BR), polatuzumab plus BR, rituximab plus gemcitabine and oxaliplatin (R-GemOx), and rituximab and lenalidomide (R2). In both the RE-MIND and RE-MIND2 studies, various sensitivity analyses were performed and supported the results of the findings.

However, a recent multicenter retrospective study that analyzed the outcomes of “real-world” tafa-len showed a markedly lower ORR, CR rate, and PFS compared to the L-MIND study [24]. In one study, 178 patients from 11 centers were analyzed. Of 149 patients evaluable for trial eligibility, 89% of patients did not meet the eligibility criteria of the L-MIND study, highlighting the gap between patients treated in the L-MIND study and patients who received tafa-len in real-world settings. The best ORR and CR
rates were 31% and 19% (compared with 60% and 43% in L-MIND), respectively. The median PFS was only 1.9 months, and patients who had refractory disease had significantly shorter PFS. This refractory patient population was not well represented in the L-MIND study. Lenalidomide initiation delays and dose reductions were common (48% and 63%), but these were not associated with shorter PFS. The inferior outcomes compared to the results of the L-MIND study were consistent across various RWE studies that analyzed the outcomes of treating DLBCL patients with tafaman [25,26]. Other studies have been conducted to describe the outcomes of recently approved treatments such as CAR T-cell therapy [13,14,27], polatuzumab-based treatment [28–30], tafasitamab and lenalidomide (tafamid) [22–24,31], and loncastuximab tesirine [32]. These RWE studies clearly show that there are often gaps between patient populations and outcomes between clinical trials and the real world.

Recently, line of treatment (LOT) specific outcomes are becoming more important, particularly for the purpose of serving as a synthetic cohort for RWE use, since trials and drug approvals are becoming more LOT-specific [33]. The Lymphoma Epidemiology of Outcomes (LEO) Consortium of Real-World Evidence (CREWE) cohort study retrospectively collected DLBCL patient data. Patients were diagnosed after 1 January 2010 and received treatment between 1 January 2015 and 15 February 2023 at one of eight academic centers in the US. The purpose of the LEO-CREWE study was to describe relapsed DLBCL patient outcomes in different lines of treatment [34,35]. The study analyzed over 1500 patients who received 2nd line (2L) or later lines of treatment; 55% of patients did not achieve CR from first-line treatment, 19% and 26% of patients achieved CR but relapsed within 12 months and after 12 months, respectively [35]. The median time from diagnosis to 2L treatment was 8.7 months. While 65% of patients who received 2L treatment intended to receive ASCT and/or CAR T-cell therapy, only 31% and 6% received ASCT and CAR T-cell therapy, respectively. With a median follow-up of 48 months after 2L treatment, the median event-free survival (EFS) and OS were 4.2 months and 18 months, respectively. The CREWE study also analyzed the outcomes of patients whose disease progressed after CAR T-cell therapy [34]. The ORR from various treatments post CAR T-cell therapy ranged from 14% when treated with chemoimmunotherapy (CIT) to 50% when treated with loncastuximab tesirine. The median PFS and OS were less than 3 months and 6 months, respectively, following the next line of treatment after CAR T-cell therapy. Although the data collection was performed retrospectively, the LEO CREWE study captures comprehensive data on evolving practice approaches over time, providing valuable resources for future studies.

2.2. Follicular Lymphoma

The National LymphCare Study (NCLS) was a cohort study conducted to describe treatment patterns and outcomes of FL in the US [36]. The NCLS study enrolled 2728 patients with newly diagnosed FL from 265 sites between 2004 and 2007. Eighty percent of patients were enrolled from non-academic sites and this cohort represented the RWD in the US. The 1st line (1L) treatment of FL ranged widely from observation (18%) and rituximab monotherapy (14%), to chemotherapy plus rituximab (52%). The study showed that there is a significant difference in treatment choice across regions of the US, and emphasized that there was no clear standard of care in FL. NCLS provided a comprehensive view of the complicated treatment landscape of FL and addressed important clinical questions such as treatment of stage I disease [37], survival outcomes of patients who are followed by observation at diagnosis [38], impact of rituximab maintenance [39], and risks and outcomes of transformed FL [40]. Also, NCLS is one of the first studies to provide references for anticipated outcomes by line of treatment in FL [41]. In NCLS, 2429 patients received 1L treatment. Of those, 889 (37%), 438 (18%), 229 (9%), and 123 (5%) patients received 2L, 3L, 4L, and 5L, respectively, with a median follow-up of 8 years. The most used regimen was rituximab combined with chemotherapy across all lines. The median PFS from 1L, 2L, 3L, 4L, and 5L were 6.6, 1.5, 0.83, 0.69, and 0.68 years, respectively. The study showed that the
median PFS reduced to less than a year in 3L+ treatment in FL. These data set the reference for future clinical trials conducted in relapsed/refractory settings [41].

In prior clinical trials, it was noted that approximately 20% of patients with FL experienced progression of disease within 24 months (POD24) after the initiation of first-line treatment. In the NCLS, patients who experienced POD24 after the initiation of first-line treatment with R-CHOP (19% of patients) had significantly poorer survival outcomes with a 5-year OS of 50% [42]. This pivotal report had a significant impact on FL research defining high-risk patients and describing their unmet needs. Since then, the importance of POD24 has been validated by many studies, including in patients who were treated with rituximab monotherapy [43], with BR [44], with R2 [45], in the modern era [46], and in phase 3 trials [43,47]. In a recent study from the FLASH group, 5225 patients from 13 pre- and post-rituximab 1L randomized trials were included [46]. POD24 was found to be strongly associated with a shorter OS by 24-month landmark analysis. The 5-year OS rates were 71.2% and 93.6% in those with or without POD24, respectively, and patients who progressed within 24 months had a three times higher risk of death compared to those who did not (hazard ratio [HR]: 3.03, 95%CI, 2.65–3.47). The GALLIUM trial confirmed the impact of POD24 on OS [47]. Following progression, the 2-year OS rate was only 20% in patients who progressed within 6 months, while the 2-year OS rate was 82.4% in patients who progressed within 24 months.

Although the definition of POD24 varies slightly across these studies, with some studies using time from diagnosis instead of time from first-line treatment, this concept established early progression as an important outcome and defined high-risk patients with FL. The SWOG 1608 trial is a phase 2 trial that randomized patients with POD24 to 2L chemotherapy, lenalidomide, or umbralisib, all combined with obinutuzumab [48]. Although the umbralisib arm was closed, this remains an important trial concept. Other trials have been developed for patients with POD24 such as ZUMA-22 (NCT05371093) [49].

Following the NLCS, several large RWE studies were conducted to describe outcomes in patients who received three or more lines of treatment (3L+) due to the focus of drug development in this arena. The SCHOLAR-5 study [50] analyzed 128 patients with relapsed/refractory FL who received 3L+ treatment at seven centers in the US and Europe between 2014 and 2020. The ORR to 3L treatment was 68% and the CR rate was 44%. The median PFS from 3L treatment was 11 months. The ReCORD-FL study was conducted in 10 centers in the US and Europe to describe the outcomes of patients with FL who received 3L+ of treatment. [51] The study collected comprehensive data from 187 patients who experienced the following: relapsed/refractory disease after 2 LOTs, including an anti-CD20 monoclonal antibody (mAb) and an alkylator; relapsed during or within 6 months post anti-CD20 mAb maintenance therapy, following at least two prior lines of therapy including both anti-CD20 mAb and an alkylator; or relapsed at any time after autologous stem cell transplantation. The index date for this study was defined as the date starting the next line of treatment after meeting the selection criteria, and thus not all patients were considered to start index treatment in 3L treatment (range, 3L–6L). The index date was required to occur between 2000 and 2018, and thus the study had a relatively long follow-up duration with a median of nine years. The ORR to the index treatment was 71%, and the CR rate was 39%. The median EFS from index treatment was 14.6 months.

An LEO CReWE study was also conducted in FL at eight academic centers in the US that analyzed 441 patients diagnosed with FL between 2002 and 2018 who received 3L+, anti-CD20 mAb, and an alkylating agent [46]. The ORR was 70% and the CR rate was 47% in 3L treatment. The ORR varied significantly by treatment from 38% for a PI3K inhibitor to 84% for CIT. The median PFS was 17 months from 3L treatment. Across these three RWE studies, treatment regimens and sequences were highly heterogeneous, confirming that there is no standard of care in FL. Survival varied significantly by risk factors such as POD24 and response to prior LOTs, and studies confirmed that response rates decreased and PFS became shorter with each subsequent LOT. Interestingly, the ORR, CR rate,
PFS were relatively similar in 3L+ treatment across the studies despite the heterogeneity of treatment, and thus serve well as a real-world historical control.

These RWE studies in FL were conducted to augment single-arm trials that evaluated novel agents such as CAR T-cell therapies and bispecific antibodies. The SCHOLAR-5 cohort was compared to ZUMA-5, which involved axi-cel [50]. Within a propensity score-matched cohort analysis between SCHOLAR-5 and ZUMA-5, axi-cel showed a superior ORR (94% vs. 50%), CR rate (79% vs. 30%), and longer PFS (median not reached vs. 12.7 months). The ReCORD-FL cohort was used to compare the results from the ELARA trial involving tisagenlecleucel (tisa-cel) [52]. The study showed superior outcomes for tisa-cel compared with standard practice. The ORR was 86% vs. 64%, the CR rate was 69% vs. 37%, and 1-year PFS was 71% vs. 52% from index treatment, and tisa-cel reduced the risk of death by 80%. The LEO CReWE cohort was compared to a trial involving the bispecific antibody, mosunetuzumab [53]. In a matching-adjusted indirect comparison (MAIC) analysis, there was no significant difference in the ORR (80% vs. 73%), CR rate (60% vs. 53%), and 1-year PFS (58% vs. 60%) between mosunetuzumab vs. RWD from LEO CReWE. Although the selection of patient populations from different RWD sources and the methodology of comparison influence the results, indirect comparison using synthetic cohorts is valuable as it provides clinical context for interpreting the results of phase 2 trials.

3. Informed Trial Design through Data Science

Trial Eligibility and Patient Selection

The demography of patients enrolled in clinical trials should ideally mirror real-world populations to enhance generalizability. However, as we discussed above, RWE studies typically show worse outcomes compared to trials. RWE studies help in understanding reasons for existing gaps in treatment outcomes between patients treated in clinical trials vs. RWD/RWE. Maurer et al. analyzed patients with DLBCL who were prospectively enrolled in the non-interventional cohort study (the University of Iowa/Mayo Clinic Specialized Program of Research Excellence [SPORE] Molecular Epidemiology Resource [MER]) and compared them to patients treated in clinical trials (LNH-2003 from the Lymphoma Study Association [LYSA] group) [54]. In the MER cohort, there were significantly more patients with high-risk features such as elevated lactate dehydrogenase (LDH) levels, poor performance status, and B symptoms; factors strongly associated with a shorter diagnosis-to-treatment interval (DTI). The DTI was significantly shorter in the MER cohort compared to patients in the LYSA LNH-2003 clinical trial programs, and a longer DTI (patients who can wait) was associated with improved event-free survival (EFS) in both cohorts. It is not only the DTI that likely affects the aggressiveness of DLBCL by high tumor burden or biology at the time of diagnosis, but patient organ function also affects trial eligibility and disease outcomes. In the MER cohort, 9–24% of patients (depending on the eligibility criteria of various trials) were not eligible for first-line treatment in DLBCL clinical trials, based on laboratory data such as CBC, kidney function, and liver function [55]. These patients who were not eligible for clinical trials also had a significantly higher risk of lymphoma-related death, and shorter EFS and OS rates compared to those who were eligible based on laboratory data. These studies indicate that the patients treated in clinical trials have more favorable characteristics yielding more favorable outcomes for both the intervention and the control arms in RCTs [56–58]. For single-arm studies, RWE studies can guide us in interpreting the results of clinical trials and clarify the importance of investigating generalizability when new treatments are applied to real-world patients.

The MER/LEO analyzed the impact of trial eligibility criteria in patients with FL [59]. The study analyzed trial eligibility in 196, 615, and 583 patients with newly diagnosed untreated stage II to IV FL from the Weil Cornell database, the MER cohort, and the LEO cohort, respectively. The study found that up to approximately 50% of patients with newly diagnosed FL might be excluded from trials based on eligibility criteria. Patients who were not eligible had higher creatinine, were older, had prior malignancy, and had more self-reported serious health conditions. However, when eligibility criteria were liberalized
to include stage II to IV instead of stage III to IV FL, a decrease in the platelet requirement from \( \geq 150,000 \) to \( \geq 75,000 \) increased the number of eligible patients by up to 20%. Patients who were eligible for trials with liberalized criteria had similar EFS rates compared to those patients who were eligible with stringent criteria. The study showed that current trials are skewed for younger patients, and stringent criteria are excluding patients for no clear reasons and likely prolonging recruitment to a trial, thus delaying drug development.

The studies discussed above show that patients treated in clinical trials have better characteristics and that the favorable outcomes seen in trials may be due to better patient selection. Also, lymphoma experts agree that many current standard eligibility criteria are not necessary [60]. RWE studies guide us to interpret the results of clinical trials and tell us the importance of investigating generalizability when new treatments are applied to real-world patients. Harnessing RWE to clarify eligibility criteria not only refines the recruitment process but also ensures that trial findings can be seamlessly extrapolated to larger, real-world lymphoma cohorts. This enhanced representativeness augments the clinical relevance and applicability of early-phase trial outcomes.

4. Innovative Trial Design Using Real-World Data in Lymphoma

The cost of conducting prospective clinical trials is increasing over time, while regulatory approval rates remain low. Moreover, the FDA’s Optimus and Frontrunner projects, initiated in 2022, encourage sponsors to incorporate randomization early in the development process in dose-expansion and phase II trials to compare experimental therapies to standard-of-care therapies. Randomized controlled trials (RCTs) are authoritative in the evidence hierarchy, and thus remain the gold standard for treatment comparison when feasible. When compared to single-arm trials, however, RCTs require more enrollment, longer patient follow-up, and additional infrastructure for institutional oversight to ensure that clinical equipoise is maintained. Moreover, RCTs tend to be more challenging to enroll in oncology settings as patients burdened by participation in trial protocols are not guaranteed to receive emerging experimental therapies that showed promising activity in prior trials.

As a compromise between feasibility and reliability, investigators have considered the utility of leveraging RWD to supplement or even replace fully randomized control cohorts. Acknowledging that fully randomized trials, while desirable, remain infeasible for many disease indications, in 2023 the FDA released a guidance document entitled, “Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products”, which provides a framework for integrating real-world and historical trial evidence into prospective trials [12]. Authors at the FDA have recently asserted that we should conceptualize such trials not as randomized versus observational, but rather over a spectrum that is defined by the extent to which the study relies on RWD. In the absence of any prospective randomization to control, externally controlled trials rely solely on comparisons to outcomes observed for RWD patients that are external to the trial itself. These trials have no mechanism for evaluating potential sources of measured and unmeasured confounding.

By way of contrast, hybrid-controlled trials (HCTs) combine prospective randomized controls with real-world controls. HCTs are implemented by imbalancing the randomization ratio to facilitate more enrollment to experimental therapies while augmenting the smaller randomized controls with eligible real-world patients treated with the trial’s control arm that exhibit clinical and prognostic characteristics commensurate with randomized trial patients [61]. Bias can be assessed statistically in HCTs, making them more desirable to regulators. Statistically modeling the “probability of cohort assignment” (trial versus external) as a function of clinical prognostic characteristics is used to elucidate imbalances in the distributions of measured prognostic characteristics. Adjusting for known prognostic factors and cohort assignment probabilities, more advanced statistical techniques (Bayesian hierarchical modeling [62,63] and frequentist robust causal inferential techniques [64]) can be applied to assess the extent to which latent or unmeasured factors explain heterogeneity.
in the distributions of outcomes between trial and real-world cohorts. Hobbs et al. established how Bayesian hierarchical models could be utilized in adaptive designs that adjust the randomization ratio in order to balance the total posterior effective sample size between the study arms in relation to the extent of evidence for bias, thereby promoting increased patient assignment to experimental therapies [65]. The development of innovative trial designs is being actively encouraged by the FDA through the Complex Innovative Trial Design Pilot Meeting Program [66]. The aforementioned Bayesian models were used to augment comparisons of overall survival in a prospective multicenter, randomized trial in DLBCL that was supported as one of the five trials accepted into the FDA’s pilot program [67]. Authors have also proposed a platform trial design for lymphoma studies which is devised to integrate historical evidence [68].

A few limitations require elaboration. Controlling measured confounding is pivotal to facilitating the interpretation of results from trials that integrate RWD. Sites contributing RWD to HCTs must adhere to strict protocols that facilitate complete and accurate reporting of patient-level prognostic and clinical characteristics, as well as therapy lines. Upon evaluating more than 200,000 NSCLC patients in real-world data sources, The Friends of Cancer Research Real-World Data Collaboration provided several guidelines that are relevant to lymphoma studies [69]. It is notable that data capture was insufficient to enable the evaluation of clinical trial eligibility in nearly 90% of these real-world patients. While date of death is measured consistently between trial and community clinics, the actual date of diagnosis or date of initiation of the therapy line may be unknown for real-world patients who may have received various lines of treatment at different clinical sites. Investigators should exercise caution when interpreting comparisons between trial and RWD for time-to-failure composite endpoints, such as disease-free survival, progression-free survival, and time to progression or recurrence, that are subject to interval censoring. In trials, these endpoints are ascertained over a strictly defined visit schedule that describes a process for adjudication by central review. The Friends of Cancer Research Real-World Data Collaboration guidelines recommend the use of real-world time to the next treatment line and real-world time to treatment discontinuation in place of the traditional interval-censored recurrence and progression endpoints often used in RCTs.

As the lymphoma treatment landscape changes rapidly, building such high-quality RWD that reflect updated current practice which can potentially serve as external control in hybrid trial design can be challenging. However, the data from studies such as LEO and LEO CReWE should meet the standard for regulatory review before consideration for such integration into clinical research [70]. With increasing importance and interest, multiple RWD sources have been developed for lymphoma, such as the REALYSA study [71]. Standardizing data collection among RWD repositories that cover and can address the heterogeneity of patients (different countries, academic settings, and communities) strengthens the validity of this research. The value of high-quality RWD will continue to rise with innovative trials devised to accelerate drug development.

5. Future Directions

Some key future directions in the evolving landscape of leveraging RWD/RWE to better clinical care include the following: (1) Enhanced Drug Development and Approval Processes: By providing insights into the effectiveness and safety of new treatments in broader, more diverse patient populations outside the controlled clinical trial setting, regulators can make more informed decisions; (2) Improved Understanding of Disease Progression and Patient Outcomes: RWE studies can offer valuable insights into real-world disease progression, patient outcomes, and long-term safety and efficacy of treatments. This can lead to a deeper understanding of lymphoma across its various subtypes and stages, informing better clinical decision-making and patient management; (3) Bridging the Gap Between Clinical Trials and Clinical Practice: RWE can help bridge the often-cited gap between the controlled environment of clinical trials and the variable conditions of real-world clinical practice. By analyzing the outcomes of treatments as they are used
in everyday practice, researchers and clinicians can gain insights into factors affecting treatment effectiveness and adherence, leading to improved care delivery; (4) Expansion of Evidence Base for Rare Subtypes of Lymphoma: Given the rarity of certain lymphoma subtypes, RWD can be invaluable in gathering evidence on these conditions, for better-informed trial design in smaller populations; and (5) Collaboration and Data Sharing Initiatives: The future will likely see increased collaboration between academic institutions, healthcare providers, and the pharmaceutical industry to share RWD and generate RWE.

Author Contributions: D.C., B.P.H. and C.R.F. designed the concept of the review paper. M.J.M. provided critical feedbacks for the paper. D.C. wrote the draft of the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: We acknowledge Rachel Anantha for editing this manuscript.


References


34. Nastoupil, L.J.; Andersen, C.R.; Ayers, A.; Wang, Y.; Habermann, T.M.; Chihara, D.; Kahl, B.S.; Link, B.K.; Cohen, J.B.; Martin, P.; et al. Effectiveness of Chemo-Immunotherapy (CIT) and Novel Therapies in Second or Later Line of Therapy (2L+) for Patients with Relapsed/Refractory (R/R) Aggressive Large B-Cell Lymphoma (LBCL). *Blood* 2023, 142 (Suppl. S1), 309. [CrossRef]


56. Hobbs, B.P.; Mandrekar, S.J.; Sargent, D.J.; Carlin, B.P.; Sargent, D.J.; Hobbs, B.P.; Mandrekar, S.J.; Carlin, B.P.; Sargent, D.J. Commensurate Priors for Incorporating Historical Information in Clinical Trials Using ABC-Type Diffuse Large B-Cell Lymphoma. *Biometrics* 2022, 78, 639–674. [CrossRef]


64. Hobbs, B.P.; Carlin, B.P.; Sargent, D.J. Adaptive adjustment of the randomization ratio using historical control data. *Clin. Trials* 2013, 10, 430–440. [CrossRef]


**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.