Including Children with High-Grade CNS Tumors in Existing Labels: The Possibilities of Real-World Evidence

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Abstract

Off-label prescriptions in the treatment of CNS tumors in children is common practice. In this study we investigate the prevalence of off-label prescribing for pediatric high-grade CNS tumors in the Netherlands and if real-world data could be used for drug label extension.

A retrospective population-based observational cohort study was performed in patients diagnosed between 2003-2017 in the Netherlands. Patient data was extracted from electronic health records. A systematic literature review was conducted on PubMed regarding possibilities and limitations of real-world data.

In first line treatment 70.3% of prescriptions were off-label. Of all prescriptions to children diagnosed with Ependymomas and choroid plexus tumors (IIIa) or astrocytomas and other gliomas (IIIb and IIId) 97.7% and 92.8% were off-label respectively. In the follow-up line treatment all prescriptions in group IIIa were off-label. Off-label prescriptions in group IIIb and IIId decreased to 44.4%.
The systematic literature review included 19 publications on RWE submissions in regulatory decision making. 12 of 19 publications provided information on 46 unique applications which used RWE. 8 of the 46 cases provided insight in extending labels to include children using RWE.

The European Medicines Agency (EMA) and Food and Drug Authorization (FDA) are making great strides advancing the use of real-world data. Real-world data has been used in post marketing surveillance and as a historical comparative arm for multiple compounds. The EMA and FDA initiated DARWIN EU and the advancing real-world evidence program, respectively. Both initiatives aim to incorporate real-world data in regulatory decision making. However, there are many challenges before real-world data can truly be incorporated. Quality and standardization of data and ethical and legal issues must be addressed. This study showed the extent of off-label prescribing in pediatric neuro-oncology. Expanding and harnessing the potential of real-world data could unlock new possibilities in extending drug labels to include the pediatric population. Currently children with high-grade CNS tumors suffer the risks of off-label prescribing. Enabling RWE and proving its value could decrease these risks.

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Introduction

Central nervous system (CNS) tumors are the leading cause of cancer-related mortality and morbidity in children.[1] In a study conducted by Ostrom et al. between 2015-2019 it was found that after diagnosis with a CNS tumor the relative five-year survival was 75.1% in the United States (US).[2] CNS tumors can grossly be divided in low-grade tumors (World Health Organization (WHO) CNS grade I and II) and high-grade tumors (WHO CNS grade III and IV).[3] High-grade CNS tumors are malignant tumors that are characterized by rapid growth. These tumors are extremely infiltrative and have a high and fast recurrence rate. [4]

Pediatric high-grade CNS tumors consist of a variety of different tumor entities but can roughly be divided into glial and embryonal tumors. The most common glial tumors are astrocytomas and ependymomas. Medulloblastomas are the most common embryonal tumors. [5] The different types of glial and embryonal tumors can be further divided into subtypes that differ in histopathology, genetics or molecular characteristics. Prognosis, treatment and outcomes vary greatly between different entities and subtypes. [6]

For example, in the fifth version of the WHO of classification of tumors of the Central Nervous System (WHO CNS5) medulloblastomas comprises four molecularly differentiated subgroups: WNT- activated, SHH-activated and TP53-wildtype, SHH-activated and TP53-mutant and non-WNT/non-SHH. SHH-activated and non-WNT/non-SHH are further divided in four and eight subgroups respectively. [3] Of these subgroups WNT-activated has the most favorable and non-WNT/non-SHH group 3 the least favorable outcome, with a 5-year survival of >95% and <60% respectively. [7][8]

Overall, treatment consists of neurosurgical resection, radiation therapy and chemotherapy. When feasible, surgical removal is the first step in the diagnostic and treatment process. The amount of tumor matter surgically removed positively influences survival. [9] However, since surgically removing the entire tumor is impossible, some malignant cells will always remain. Therefore, radiation- and/or chemotherapy is a necessary follow-up treatment to remove remaining tumor cells. Radiation therapy is effective, but the downside of radiation therapy are the severe long-term neurological complications it causes in children.[10][11] Due to the negative effects of radiation therapy, research and use of chemotherapy has increased over the years. Chemotherapy plays an important role in the treatment of CNS tumors, as it reduces the need or amount of exposure to radiation in children.[10][11] Moreover, there is no fit-for-all treatment due to heterogeneity of the population. Therefore, a vast array of different chemotherapies may provide the best possible treatment for many. [6] However, chemotherapy is often prescribed off-label, leading to treatment differences in and between countries, but also nationally. [12]

Off-label prescription of drugs to children has been prevalent throughout the years and around the world. For example, Balan et al. conducted a literature review on off-label prescriptions in various countries. They found that between 1.2% and 99.7% of prescriptions were off-label, depending on ward and country. This study was limited as it did not include for which drugs and indications off-label prescribing was highest, but it does highlight the problem of off-label prescribing. [12] The Dutch Pediatric Formulary (DPF) provides information on indication and dosing for drugs both approved and off-label specifically for the pediatric population. In a review conducted by van der Zanden et al., it was investigated what the number of off-label records and the quality of evidence justifying the off-label use was. A record was defined as encompassing a specific drug, indication and age group. Among others, 67 antineoplastic and immunomodulating agents were analyzed encompassing 541 records of which 233 (43.1%) were off-label. Only 23 records were supported by high quality evidence leaving 210 records poorly supported. The review concluded that research on supporting off-label drugs should be increased. [13]

Although data on off-label drug prescription for children is available, data regarding the treatment of pediatric cancer is virtually non-existent. However, when investigating the adult population, Saiyed et al. found that 13%-71% of adults treated for cancer received at least one off-label prescribed chemotherapy. [14] In general children are included in fewer labels of authorized drugs this would suggest a similar or increased trend for the pediatric population. A study conducted by Lim et al. in a pediatric cancer center which found that the prevalence of off-label use increased from 2007-2017. ~2% of targeted therapies in 2007 were used off-label, while in 2017 this increased to ~13%. It should be noted that patients aged 30 years and younger were included, despite the research being conducted in a pediatric center. [15]

Off-label prescribing for children is inherently accompanied by risks such as a lack of dosing information supported by high quality evidence. Pharmacovigilance is enforced to a lesser degree. This can both increase the risk of adverse drug reactions (ADRs) occurring. [12][13][16][17] Another problem is that off-label prescriptions are not always reimbursed, with reimbursement differing between countries and insurance companies. There are differences between the healthcare systems in Europe and the US. In Europe for instance medical expenses are almost always covered for 100%, [18] whereas patients in the US often face lower coverage and high out-of-pocket costs [19] . However, for both Europe and the US reimbursement of off-label prescriptions are a gray area. Reimbursement is dependent on several factors, such as approval of the off-label “indication”, the cost associated with treatment and the availability of suitable alternatives.[19][20] This incoherence can influence off-label prescription and overall treatment of patients.

Despite the risks, off-label prescribing in children remains common practice for different reasons. For example, there is a lack of clinical trials that include children and therefore no pediatric

indication is included for the drug product. Reasons for having few trials including children are both practical and ethical. Pediatric trials have a higher chance to be underpowered due to a smaller sample size and a more diverse response to the treatment. Consequently, the results may lack any statistical significance causing the trial to not have any added value. The ethical aspect of conducting trials with is that children cannot understand potential risks and rely on adults to make this decision for them, a responsibility which the adult in question may find discomforting. [21] The uncertainty if a pediatric trial will provide tangible results lead to most pharmaceutical companies being hesitant to conduct them. The probability of wasting time and resources is high, while the possibility of generating significant results is low. [14][21]

This problem was also noted by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). To increase studies in children the EMA has made it mandatory for pharmaceutical companies to provide a Paediatric Investigation Plan (PIP) when applying for a new drug or indication. The PIP must contain information on how data will be collected through studies in the pediatric population to investigate possible usage of the drug in children. Companies which complete a PIP are rewarded with an extension of the patent by 6-24 months. [22] The FDA manages a different approach, with a Pediatric Study Plan (PSP) being mandatory for new drugs and indications if the indicated population are adults and children. The reward for completing a PSP regardless of outcome is a six-month extension of market protection for every product containing the active ingredient. [22] However, currently the completion rate of PIPs and PSPs is still low. In a study conducted by Hwang et al. it was found that of the 326 PIPs from 2010-2014, only 38% were completed by 2017 after a median-follow-up of 7 years. [23] In another study conducted by Hwang et al. it was found that out of the 222 FDA mandated PSPs from 2007-2014 only 33.8% were completed by 2017 after a median follow-up of 6.8 years. [24]

Therefore, this study aims to describe the type and prevalence of off-label anticancer drug use in children with a high-grade CNS tumor in the Netherlands. Furthermore, we aim to investigate the potential role of real-world data (RWD) as a primary source of data in the label extension process to broaden adult indications of anticancer drugs to include pediatric patients.

Methods: off-label prescription analysis

Study design and setting

This retrospective population based observational study included all patients aged 17 years or younger diagnosed with a high-grade CNS tumor (WHO CNS grade III and IV) diagnosed between 2003 and 2017 in the Netherlands.

Data were obtained from the Netherlands Cancer Registry (NCR) and were coded according to the International Classification of Disease for Oncology (ICD-O), which is used to code disease data for cancer registries. [25] Since 1989 this registry is maintained by the Netherlands comprehensive cancer organization (IKNL) covering the entire Dutch population. The data obtained for this study was extracted from electronic health records (EHR) by trained registrars with expertise in neuro-oncology.

Selection of cases and definitions

We categorized the included patients, according to the International Classification of Childhood Cancer (ICCC-3), into 5 main groups of CNS tumors based on their ICD-O morphology code. These are, (IIIa) Ependymomas and choroid plexus tumor), (IIIb and IIId) Astrocytomas and other gliomas, (IIIc) Intracranial and intraspinal embryonal tumors, (IIIe) Other specified intracranial and intraspinal neoplasms or (IIIf) Unspecified intracranial and intraspinal neoplasms. [26] The patients were further stratified according to their age group, which are, 0-3, 4-9, 10-14 and 15-17. Diagnostic groups (IIIb) and (IIId) were merged because of pathological similarities and overlapping ICD-O codes. The age group 0-3 was chosen as temozolomide has an indication for patients 3 years and older.

Categorization on-/off-label prescriptions

On-/off-label prescription was based on 3 reference sources, that is, the Summary of Product Characteristics (SmPC), Informatorium Medicamentorum and the Dutch Pediatric Formulary (DPF). Based on these sources, a drug was considered to be prescribed off-label if it had no registered (pediatric) indication or if the indication was for an indication other than CNS tumors.

Analyses

Descriptive analyses were conducted for main indication, age group, drugs prescribed and on-/off-label prescription. Every main indication was subdivided in the four age groups. For each group the number of prescriptions was analyzed. The analyses were performed using Rstudio version 4.0.3. [27]

Methods: real-world data in regulatory approvals

Systematic literature review

In this study a systematic literature review was conducted in PubMed to identify publications on the use of real-world data in regulatory drug approvals, focusing on the role of RWE submitted pre-authorization in marketing authorization applications and extension of indication applications. Our search focused on studies referencing applications to the FDA and EMA.

The search string was composed of free text terms and medical subject headings (MeSH) for real world data, real world evidence, observational data, FDA, EMA, International Court of Harmonisation and drug approval. The complete search string is present in the appendix of this paper, see appendix 1.

The publications were screened by LB. First the titles were screened on relevance and if it showed relevance, it was provisionally included. Second, the abstracts of provisionally included publications were read, removing irrelevant publications. Finally, the remaining provisionally included publications were proofread and assessed for eligibility.

Inclusion and exclusion criteria

The search was restricted to articles published in the English language in PubMed, without a restriction on publication date, which studied the use of RWD in regulatory drug approvals. We included publications concerning other regulatory agencies. We included, systematic reviews, case reports and original research papers. We excluded publications discussing medical devices, post approval safety/efficacy studies, Health Technology Assessment (HTA) or reimbursement studies, studies discussing generating of RWD and studies lacking a clear RWD/RWE component.

Data extraction

Data was extracted in a standardized table using the following columns: author/date, title, which regulatory agency, does it concern an initial drug or label extension approval, is the approved drug for adults or children, what drug and the role of RWD/RWE is submitted for the drug application and the therapeutic area.

Outcome

The main outcome of this part of the study was to provide an overview of how RWD/RWE have been used in regulatory approvals of drugs.

Results: off-label prescription in children with high-grade CNS tumors

First line treatment cohort characteristics

In total 819 cases who received first line treatment were defined between 2003 and 2017, of which 812 were eligible for use in the analysis. Figure 1 shows the enrollment process of the patients Seven cases were removed because they were duplicates (n=5) or contained missing information (n=2). Table 1.1 shows the patient characteristics of the 812 included patients.

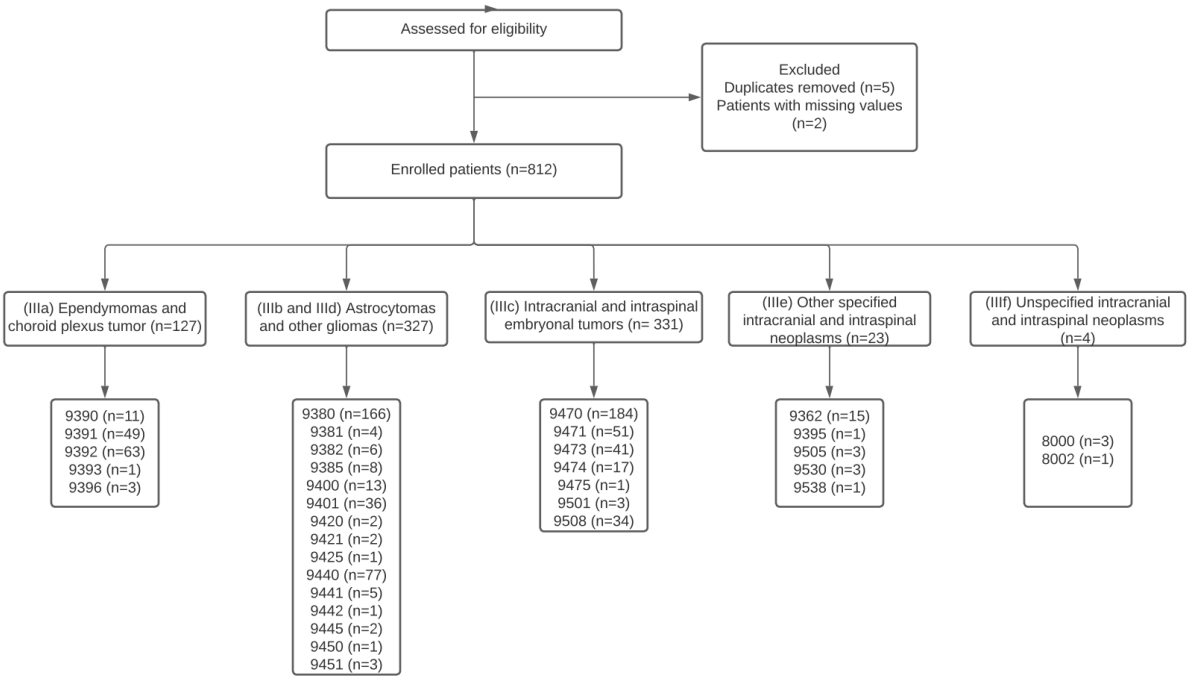


Figure 1: Flowchart of enrolled patients and their diagnosis

Follow-up treatment cohort characteristics

Another 618 cases who received treatment after first line were defined from the same patient pool. These patients were pooled together under follow-up treatment, figure 2 shows the number of patients per line of treatment. Of these 618 cases, 577 cases were deemed eligible to be included in the analysis. 41 cases were removed due to missing information on diagnosis (n=40) or treatment (n=1). Table 1.2 shows the patient characteristics of the 577 included patients. All patients were treated in the Netherlands.

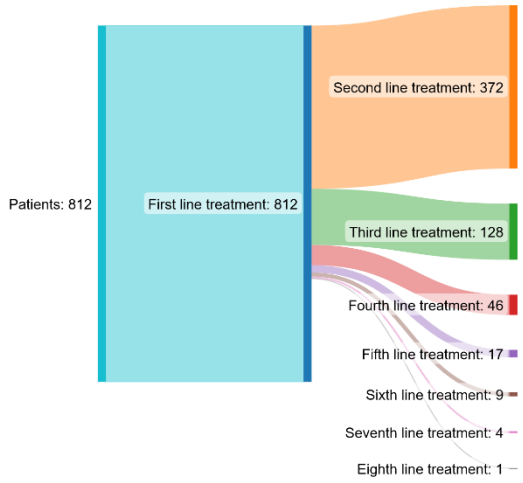


Figure 2: Cases stratified per line of treatment

First line off-label prescriptions

An overview of the top ten drugs prescribed in the first line table 2. The overview gives the total prescriptions and whether they were prescribed on- or off-label. The top ten drugs were prescribed 1470 times in the first line of which 1034 (70.3%) were off-label. 127 (15.6%) patients were categorized in group IIIa and received 131 prescriptions of which 128 (97.7%) were off-label. 104 (79.4%) of these prescriptions were prescribed to children aged 0-3. 327 (40.3%) patients were categorized in group IIIb and IIId and received a total of 138 prescriptions of which 128 (92.8%) were off-label. Another point of interest was that 67 (48.6%) prescriptions were for temozolomide which is off-label in the first line. The largest group of patients were categorized in group IIIc and received 1140 prescriptions of which 724 (63.5%) were off-label. Vincristine was prescribed in 263 (23.1%) cases across all age groups. Platinum-based drugs Cisplatin and Carboplatin were prescribed 219 (19.2%) and 131 (11.5%) times respectively. Temozolomide got prescribed 20 (1.75%) times.

Follow-up off-label prescriptions

An overview of the top ten drugs prescribed in the follow-up line are given in table 3. In the second line and onwards 442 drugs were prescribed of which 351 (79.4%) were off-label. 124 (21.5%) patients of group IIIa received follow-up treatment which totaled 69 prescriptions, all off-label. 220 patients of group IIIb and IIId 220 (38.1%) received a follow-up treatment. In total 126 drugs were prescribed of which 56 (44.4%) were off-label. Temozolomide was prescribed 65 times, 5 (7.9%) prescriptions were off-label. 213 (36.9%) patients of group IIIc received follow-up treatment. A total of 225 drugs were prescribed of which 210 (93.3%) were prescribed off-label. Vincristine and Temozolomide were prescribed 15 (6.7%) and 57 (25.3%) times respectively. Cisplatin and carboplatin were prescribed 16 (7.1%) and 8 (3.6%) times respectively.

Results: Systematic literature review

Our search identified 680 unique publications, after screening 41 articles were included for proofreading the full text. In total 19 articles met our in- and exclusion criteria. Figure 3 shows the full selection process of the publications.

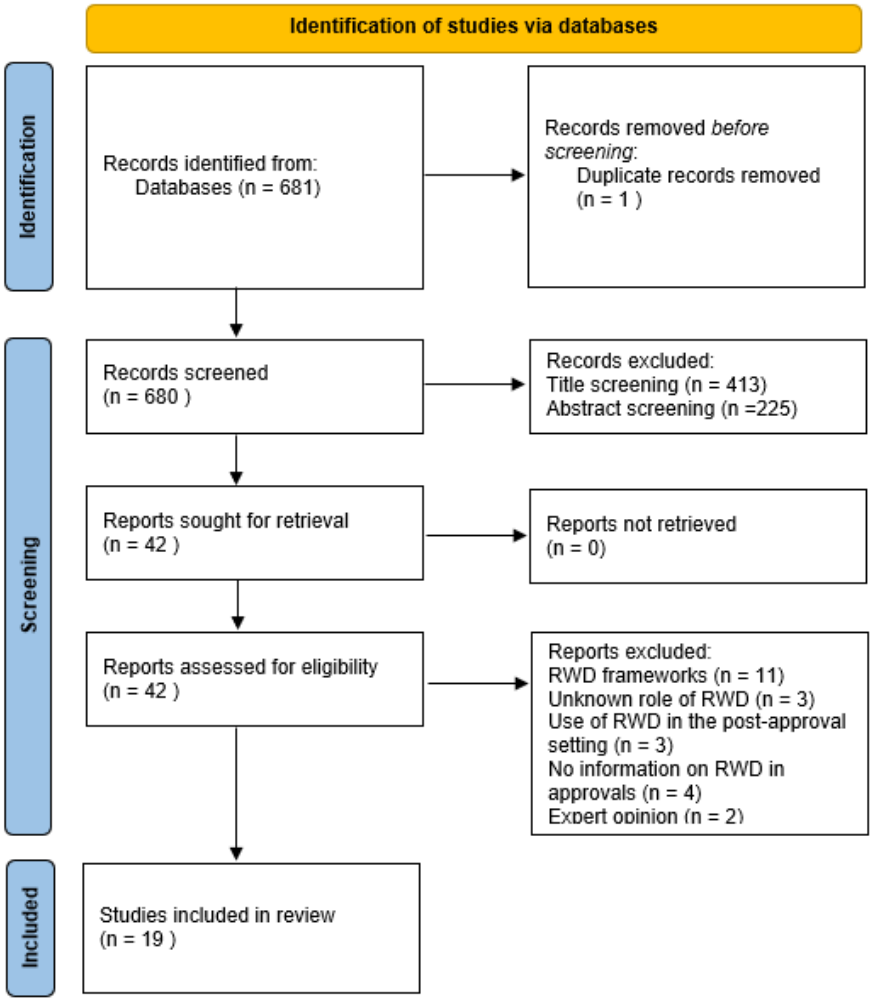


Figure 3: Systematic review process flowchart

RWE in drugs authorized by the FDA

Table 4 gives a summary of all included articles discussed in the results. This and the following 2 subheadings give information about the publications which lacked data on specific drugs, but instead studied the role of RWE in regulatory decision making in a large pool of (un)authorized drugs. This is followed by the results of 12 publications which do contain information on specific drugs.

A study conducted by *Mahendraratnam et al.* in 2021 evaluated the submission of RWE to support efficacy to the FDA. The evaluated period was between 1954 and 2020 and they identified 34 cases where RWE was submitted to support efficacy. 7 submissions followed the passage of the 21st century cures act in 2016 and 13 after the release of the FDA RWE framework in 2018. In 9 (26%) approved drugs the indication was for oncology of which 2 (22%) drugs got an extension of label in oncology and 2 (22%) approved drugs were for an oncology indication in the pediatric population. [28]

In 2022 a similar study was conducted by *Purpura et al.* to evaluate the role of RWE in FDA approved new drug applications (NDAs) and Biologics license applications (BLAs). The study found that 136 applications were approved between 2019-2021 of which 83 (61%) incorporated RWE to provide therapeutic context and 88 (65%) applications incorporated RWE to support safety/efficacy. 57 (65%) drug applications provided supporting RWE and 8 (9%) drug applications provided primary RWE used in the decision-making regarding safety/efficacy. In total 30 approved drugs which included RWE had an indication in oncology. [29]

RWE in drugs authorized by the EMA

In 2021 *Flynn et al.* conducted a similar study, but for applications to the EMA. This study found 158 Marketing authorization applications (MAAs) and 153 Extension of Indications (EoIs) approved by the EMA between 2018-2019. In the case of 63 (39.9%) MAAs and 28 (18.3%) EoIs, RWE was submitted in their application. With 20 MAAs (12.7%) and 16 (10.5%) EoIs submitting RWE studies pre-authorization, consisting of 5 primary and 17 supportive RWE studies and 4 primary and 12 supportive respectively. Of 36 MAAs and EoIs RWE was submitted for safety in 27 (75%) cases and for efficacy in 27 (75%) cases. The majority of approved MAAs (n=23) and EoIs (n=12) including RWE were for oncology. [30]

A study conducted by *Eskola et al.* investigated the RWE signature of 111 medicinal products approved by the EMA between 2018-2019. It was found that RWE was used across several stages of drug development. The stages were defined as: 1. Discovery, 2. Early development, 3. Full development, 4. Registration/market access and 5. Lifecycle management. 8.1% of applications

submitted RWE in full development, which was subdivided in trial design, efficacy and safety. 5.4% of applications submitted RWE in registration/market access to study effectiveness. 30 approved drugs concerned oncology of which 13.3% used RWE in full development and 6.7% in registration/market access. [31]

Differences in use of RWE between regulatory agencies

A study conducted by *Bolislis et al.* collected cases in which one or several regulatory agencies approved an initial or label extension application where RWE was associated with the regulatory decision. This study found that 17 NDAs and 10 EoIs were approved by the EMA, FDA, Health Canada or Japan PMDA up until 2019. The collected cases showed that there are some discrepancies between the regulatory agencies of different countries. The EMA and FDA approved 13/7 and 11/8, NDAs/EoIs respectively. Health Canada and Japan PMDA on the other hand only approved 3 and 2 NDAs respectively. Further discrepancies lay in the fact that some dates when the drugs were approved differ by quite a margin. For example, carglumic acid was approved by the EMA (2003), FDA (2010) and Health Canada (2015). Furthermore, only the EMA has withdrawn some of their approvals (Zalmoxis, approved 2016, withdrawn 2019). [32]

Lau et al. Conducted a study which compared the use of RWE in approved drugs, with an oncology indication or a non-oncology orphan drug designation, by the EMA, FDA and Health Canada between 2020-2021. The FDA and Health Canada both approved 29 oncology drugs and the EMA approved 25 of 29 oncology drugs. Of these approved drugs 24.1%, 75.9% and 56.0% were submitted with RWE to Health Canada, FDA and EMA respectively. Health Canada approved 21, FDA approved 19 and EMA approved 17 non-oncology orphan drugs. The percentage of these approved drugs 36.8% (Health Canada), 68.4% (FDA) and 64.7% (EMA) were submitted with RWE. [33]

Role of RWE

Over the past few years both the EMA and FDA have approved quite some drug applications, but only a fraction of these submitted RWE (pre-authorization) as evidence. Bloomfield-Clagett et al. conducted a study and found that the FDA approved 30 new drugs (neurology related) between 2019-2021, 3 applications contained RWE. [34] Bakker et al. and Flynn et al. conducted 2 different studies using the same data and found that the EMA received 311 MAA and EoI applications of which 91 submitted RWE. Less than a third used RWE pre-authorization and most often as supportive evidence. RWE was most often used in a cohort study as an external control, studying drug epidemiology or drug utilization. RWE was commonly extracted from EHRs and registries. [30][35]

In the study conducted by Lau et al. it was found that the EMA and FDA used RWE as external controls in ~20% of the applications while Health Canada did not use RWE as external controls. [33]

The study conducted by Mahendraratnam et al. found that of 34 approved drugs by the FDA that submitted RWE, 20 used it as an external control. [28] RWE studies are usually a supportive role and often as an external (historical) control to an intervention group.

Table 5 contains key information from publications (n=12) which covered specific cases of initial or extension approvals including RWE authorized by either the EMA or FDA. In total 66 cases are mentioned across the publications, when duplicates are removed 46 unique cases remain. The majority of cases are applications for initial drug approvals (n=35) while extension applications (n=11) were less numerous. The applications were submitted to the FDA in 37 of the case reports and the 19 applications were submitted to the EMA. Of 46 applications the indicated population were children (n=4), adults (n=16), adults and children (n=24) and unknown (n=2).

There were 35 initial drug applications with an indicated population of children (n=3), adults (n=15) and both adults and children (n=17). Of the 11 extension of label applications the indicated population comprised children (n=1), adults (n=1), both adults and children (n=7) and unknown (n=2). Of all label extensions, in which children were included, Blincyto was the only one with an indication in oncology. For both initial and extension of label applications RWE was mostly in a supportive capacity (n=21), with RWE often providing external (historical) comparators.

In 2019 *Jandhyala* conducted a study on ''The effect of adding real-world evidence to regulatory submissions on the breadth of population indicated for rare disease medicine treatment by the European Medicines Agency''. Although not significant it was found that applications containing both RWE and RCT data, opposed to only RCT data, had a broader indicated population in ~20% of the cases. It was predicted that between 2032-2037 studies will have sufficient power to tell if RWE has an effect on broadening the indicated population of applications. [36]

Case examples

A prime example of the use of RWE as primary evidence is the approval of cerliponase alfa (Brineura) by the EMA and FDA in 2017. It is used to treat neuronal ceroid lipofuscinosis type 2 (CLN2) disease, which is a form of Batten disease. Before Brineura was approved there was no treatment available for this rare disease. Due to the low prevalence of CLN2 Brineura's efficacy was tested in a nonrandomized, single-arm, open-label, dose escalation trial. The study population was composed of 24 pediatric patients with CLN2. Due to the small sample size and ethics the study was not placebo-controlled and thus RWD was used to provide an external control group. The external (historical) control cohort consisted of 42 untreated CLN2 patients with comparable patient characteristics as the study population. Data on the external control group were extracted from a

natural history registry. The two groups were matched according to similar characteristics to account for confounders such as age and genotype. In total 17 matching pairs were formed and various analyses were conducted to provide evidence on Brineura's efficacy. The data from these analyses irrefutably proved the efficacy of Brineura which led to its approval. [37][38][39]

Blinatumomab (Blincyto) is a drug with 2 examples regarding the use of RWE for approval. Firstly, for its initial approval and secondly for an extension of label. Blincyto was initially approved for the treatment of Philadelphia chromosome-negative relapsed and/or refractory B cell-precursor acute lymphoblastic leukemia (FDA 2014, EMA 2015). The approval of Blincyto was based on a single-arm phase II study which assessed safety and efficacy of the treatment. This study and its results were compared to an external (historical) control group. The data of the external control group were extracted from American and European databases. Analyses conducted between the two groups supported the initial evidence and approval of Blincyto.[39][40] Blincyto later received an extension of indication to include B-cell precursor acute lymphoblastic leukemia. (FDA 2018, EMA 2019). This extension was based on the open label, single-arm BLAST-study which was compared to an external (historical) control group. The comparison found a significantly longer relapse-free survival in patients treated with Blincyto than patients from the external control group. This evidence eventually contributed to the extension of indication of Blincyto. [39][41][42]

There are also cases where RWE was found to be inadequate to support an application, as was the case with Selinexor (Xpovio). Xpovio's safety and efficacy was evaluated in the open label, single-arm STORM-trial. Objective response rate, duration of response and overall survival were endpoints of the trial. RWE was used in a retrospective observational study using EHR data. The intention was to compare overall survival between the STORM-trial and the observational study. However, the FDA found methodological flaws in the use of the EHR data. In turn the FDA conducted their own analyses and concluded that the sample size was too small, patients were not comparable and the estimates of overall survival uncertain. The results of the study were deemed subpar and were not used in the decision making. [41][42][43] However, Xpovio was later approved by the FDA in 2019 when the applicant submitted the phase III BOSTON-trial. [42]

Discussion

In first line treatment 1034 (70.3%) prescriptions and in follow-up treatment 351 (79.4%) prescriptions were prescribed off-label to the pediatric population with CNS tumors. Cisplatin (241), Cyclophosphamide (214), Carboplatin (195) and Etoposide (193) were most often prescribed off-label in first line treatment. Etoposide (96), Temozolomide (79), Cyclophosphamide (38) and Carboplatin (31) were most often prescribed off-label in follow-up treatment. In first line treatment, age groups 0-3 and 4-9 received 460 and 402 off-label prescriptions respectively. This decreased to 134 and 150 off-label prescriptions in follow-up treatment. in both treatment groups, patients with these ages received the most off-label prescriptions.

In our systematic literature review we found that applications to both the EMA and FDA mostly concerned initial MAAs indicated for the adult population and used RWE in a supportive role. Applications for an EoI were less common and when present were often to broaden the indication of the adult population. Approved MAAs or EoIs of which the indication included children often did not include the entire pediatric population but a portion of it. Furthermore, it was found that it could take to 2032-2037 for RWE to have a significant impact in broadening the indicated population. [36]

Prescribing drugs off-label is common practice in the Dutch pediatric population diagnosed with high-grade CNS tumors. Our systematic literature review reveals that most initial MAAs and EoIs use RWE in a supporting role and are used to broaden the indicated adult population. This can partially explain off-label prescribing in the Dutch pediatric population. However, there are certain cases in which RWE is used in a primary role to extend the label to include children which could be used as an example. At present there is an urgent need to extend existing labels to include the pediatric population. Off-label prescribing is accompanied by a lack of dosage information backed by high quality evidence, lesser degree of pharmacovigilance and increased risk of ADRs. [12][13][16]

Furthermore, the indications of label extensions we would like to see do not change, only the breadth of the population. An extension of label does not need to prove safety/efficacy for another indication, it only needs to include children. This means the initial pivotal trials will for the most part still hold up and only a little more data on safety/efficacy in children is necessary. In addition, many drugs are already prescribed off-label in the pediatric population, which could retrospectively be studied to (dis)prove safety/efficacy.

Applicants are already obligated to conduct PIPs (EMA) or PSPs (FDA) to investigate possible uses of drugs in the pediatric population. However, the completion rate is not what it could be, possibly excluding children from existing labels unnecessarily. [23][24] RWE studies could possibly help close this gap and increase the extension of labels. In studies conducted by Purpura et al.[29], Flynn et al. [30], Lau et al. [33] and Bakker et al.[35] it is shown that RWE can and is used in initial and label

extension applications. This shows that there are possibilities to meet the, as of yet, unmet demand of extending labels to include children.

Regulatory agency programs

EMA

Our study shows that RWD is already used by pharmaceutical companies in a mainly supportive role regarding MAAs or EOIs. However, since the COVID-19 pandemic the EMA realized that RWD can prove extremely useful in providing great quantities of information on safety and efficacy of a novel drug. This realization was the cause for the EMA to research and improve the use of RWD and RWE. In 2020 the EMA published the European medicines agencies network strategy towards 2025 which contains key goals and objectives regarding the use of RWD and RWE in the future. [44] The first goal is ''Enable access to and analysis of routine healthcare data, analysis of individual patient data from clinical trials, and promote standardization of targeted data''. To enable access to RWD the Data Analytics and Real World Interrogation Network (DARWIN EU) was launched. This is a platform from which healthcare data can be accessed by members of the EU. [44] To enable DARWIN EU the EMA is working on a data quality framework for all data, including RWD, on regulatory decision making and improving the discoverability of RWD. [45] DARWIN EU promotes the use of RWD for post-approval studies/analysis. RCTs are the standard to generate evidence on safety and efficacy, but it does not always reflect the real-world population. The EMA sees RWD to be used post-approval to complement data gathered through RCTs. Furthermore, the EMA is interested in how in the future RWE can be more often utilized as a historical comparative arm for rare indications. [44] To make sure data and access to it are widely available the EMA wants to establish further collaborations with external stakeholders and international regulatory authorities. [44] The second goal is to ''Build sustainable capability and capacity within the Network including statistics, epidemiology, real world data and analytics''. The EMA acknowledges that the gathering of RWD is evolving rapidly and to use this data accurately and efficiently they need to be able to analyze big data. Their plan is to digitalize and modernize their processes and create a digital infrastructure, capable of utilizing the vast amounts of data. Optimizing and automating existing processes and make uses of new digital tools and AI to process RWD. Increasing the Networks capabilities to process data is needed to utilize RWD to its full potential. Models and simulations are already used extensively in regulatory decision making, but the increased capability is needed to use these models for subgroups such as children. [44] The third goal is to ''Promote dynamic regulation and policy learning within the current regulatory framework''. The European Union consists of many different countries with varying levels of digitalization and how they collect data. The EMA wants to optimize interaction and standardization between its member states. The fourth goal is to ''Ensure that data

security and ethical considerations are embedded in the governance of data within the Network''. Increasing the gathering and usage of RWD has the potential to be very helpful, but if mismanaged or used improperly it can also be harmful. With technological advancement and authorization to use data of every patient ethical and legal issues need to be addressed. The EMA wants to keep public and stakeholder support and trust, so the future framework also contains rigid guidelines to ensure proper handling of privacy and ethics concerning patient data. [44]

FDA

In 2016 the 21st Century Cures Act was signed into law by the US government. This law was meant to expedite the development of drugs as well as delivering new innovations and advances to the patients in need of them. To accomplish this the FDA has created a framework to evaluate the potential RWD/RWE may provide in supporting approval of new indications for approved drugs or how it can be used in the post-approval setting. As of now this framework is still being used in developing guidelines and strategies.[46][47]

More recently, October 20 2022, the FDA started their Advancing Real-World Evidence Program. [48] This program continues on the path the original framework laid out. [46] The program was established to improve quality and acceptance of RWE used to support label extensions or in post-approval studies. The program gives companies the opportunity to meet with FDA staff before developing their protocol or initiating a study to discuss how RWE can be of use in developmental process. Meetings under the advancing RWE program will be conducted from 2023-2027. This way the FDA tries to encourage and regulate the use of RWE by stakeholders. The program is designed with three goals in mind. The first goal is to "identify approaches for generating RWE that meet regulatory requirements in support of labeling for effectiveness (e.g., new indications, populations, dosing information) or for meeting post-approval study requirements". One of the major complications of RWD is no standardized format. This makes it harder for RWE to meet regulatory requirement, because this has not yet been properly defined. The program seeks to explore approaches and standards to make this easier. The second goal is to ''develop agency processes that promote consistent decision-making and shared learning regarding RWE''. As well as standardization of gathering RWD there needs to be a standard for processes to ensure consistency in regulatory decision making. Secondly the FDA tries to attract different stakeholders so together they can give form to this standardization. The third goal is to ''promote awareness of characteristics of RWE that can support regulatory decisions by allowing FDA to discuss study designs considered in the Advancing RWE Program in a public forum''. As mentioned before there are still many applications which do not make use of RWD or RWE to support their study and much can be gained if this would increase. The program aims to increase awareness of RWD and RWE and the possibilities it may

offer. Promoting and holding these meetings and providing a public forum has the potential to advance the use of RWD and RWE. [48]

RWE fit for regulatory purpose

In recent years the amount and availability of RWD, and therefore the potential to generate RWE, expanded greatly. As discussed before numerous agencies and stakeholders see the potential in using this data to generate evidence to support regulatory decision making or studies. However, ''raw'' RWD by itself is not enough to generate usable RWE. To generate fit-for-purpose RWE, fit-for-purpose RWD is needed. To determine if RWD is fit-for-purpose depends on the regulatory question which needs to be answered. Daniel G et la. Of the Duke Margolis Center explain that to generate RWE which is fit-for-purpose depends on four different factors. What is the regulatory question, in what clinical context will RWE be generated to answer this question, is there enough RWD available of high quality and relevancy to generate RWE and finally are there suitable and proven methods to turn this RWD in RWE. [49] Relevancy of data is also codependent on the intended research question. Once a question is formulated available RWD needs to be evaluated on relevancy and quality to determine if the data is fit-for-purpose to support a regulatory decision. For data to be relevant it needs to contain information representative of the population which is studied. The dataset should contain information on the relevant population, exposure, covariates and outcomes or should be at least derivable from other variables. If information from multiple data sources is used the data is only relevant if their data is compatible and can be linked. The last dimension in evaluating relevancy is an appropriate amount of included persons and follow-up time. However, relevancy alone is not enough to determine fitness of the data. High quality of the data is also a necessity. Data quality is determined by accuracy, completeness and transparency. Data quality addresses the possibility of information bias which could negatively influence the validity of the data. High quality data is accurate, consistent and conforms to internal and external standards. Furthermore, transparency is also important for the determination of fitness of data. Information on where the data is derived from and when the data was extracted should be provided. [46][49] Gatto et al. used the framework of the Duke Margolis Center (DMC) as the basis to expand on.

According to Gatto et al. researchers are under time pressure when investigating questions regarding safety/efficacy which are intended to inform regulatory decisions. Considerations such as contracting logistics, data access time and time to completion are important when selecting the proper dataset to provide RWE. Gatto et al. created a framework which provides a step-by-step process/tool for researchers to find the correct dataset for their question. [50] For our dataset to be relevant it needs to comply with 3 out of 4 dimensions provided by the DMC. We can exclude the dimension regarding multiple data sources, since we only used 1 data source. [49] First, our dataset does represent the study population of interest and includes a sufficient amount of patients to

comply with 2 dimensions, namely representativeness and sample size. The third dimension requires the dataset to provide key information on exposure, covariates and outcomes. Our dataset does not contain information in all these critical data fields. For one our dataset provides information on what treatment patients received, but misses information on dosage or treatment regimen. Secondly, important covariates such as possible polymorphisms and kidney and liver functions are unknown. Lastly, outcomes such as possible safety risks (ADRs) or efficacy of a specific treatment(regimen) are not present in our dataset. Data quality contains the 3 dimensions: accuracy, completeness and provenance. The data is accurate, but lacks completeness. The provenance and transformation of the data by NCR registrars were transparent. Considering the DMCs dimensions on data relevancy and quality our dataset is not fit-for-purpose to extend existing labels to include children.

Limitations of RWE

RWE has great potential to assist in regulatory decision making, but as with all study designs it has a selection of strengths and weaknesses. RWE studies are susceptible to the introduction of biases due to overlooked confounders. In the real world a physician prescribes a treatment with the highest expected benefit to a particular patient. Patients who receive a particular effective drug in the real world may differ from those who do not, which can introduce selection bias. This can make it challenging to draw meaningful conclusions about the drugs safety and efficacy. [51][52]

Unlike RCTs, RWE studies do not involve randomization, which is considered the gold standard for establishing causal relationships. Without randomization and because of the retrospective nature of RWE studies, it is harder to control for unknown or unmeasured confounders. Unknown beneficial or harmful factors might influence the outcome, without the researcher's knowledge. A better outcome for one group may well be caused by this imbalance of confounders and not because of the intervention. [51][52]

Datasets used in RWE generation are susceptible to manipulation through omitting undesirable data or misclassification of data. On top of that analysts can conduct a series of different analyses using the same RWD until a beneficial outcome is singled out, with analyses yielding undesirable outcomes being omitted. This so-called cherry picking to prove a set conclusion can greatly distort the real benefit or harm of a treatment. Regulators are still developing guidelines and standards for the use of RWE in drug approvals. The lack of standardized methodologies and criteria enables cherry picking RWD. [51]

External historical control arms also have their limitations. Historical control arms influenced by changes in medicine, treatment guidelines, and external factors over time. A study conducted by Sacks et al. found that 80% of historical control studies conducted the intervention of interest was superior to the control intervention. [53]

Strengths of RWE

RWE serves as a valuable tool for comparing assessments of different interventions within real-world settings. It is characterized by a lack of close patient monitoring and treatment adherence enforcement, differing from the controlled environments of RCTs. This utility is particularly pronounced when the study's objectives encompass evaluating the endurance of intervention effects, their generalizability, and long-term safety profiles. [51][54]

RWE studies allow for the inclusion of a broader and more diverse patient population than traditional RCTs. This can provide insights into how a drug performs in real-world scenarios and in populations that may not have been well-represented in RCTs. Excluded or under-represented populations in RCTs, such as pregnant women and the pediatric population, can be included in observational retrospective studies without the ethical complications of a RCT. This potential to provide evidence on safety/efficacy in these study populations is a great asset of RWE studies. [54]

In contrast to RWE, RCTs typically have a duration and study population and may not capture long-term safety and effectiveness data. RWE can provide insights into the long-term outcomes of drug use, which is especially important for chronic conditions or drugs that are intended for long-term use. In addition, being able to analyze vast study populations over extended time periods RWE studies can better detect rare or unforeseen endpoints which occur infrequently, than RCTs. [51][54]

The average cost of a phase III clinical trial is 33 million US$, with an average of ~40% being spent on personnel alone. Increasing the number of sites, subjects, countries and duration has a direct effect on total cost of a clinical trial. Increasing trial duration by one month costs on average 671,000 US$. [55] RWE studies do not share the same burden as clinical trials regarding costs. The amount of personnel needed to conduct a RWE study is far fewer than in a clinical trial and increasing any of the aforementioned factors do not increase the cost of conducting a RWE study in the same way as a clinical trial. A major strength of a RWE study is the lower cost, making it more feasible to conduct one or more studies to generate evidence. [51][52]

RWE can be generated relatively quickly, allowing for timely decision-making and adjustments to drug approvals based on emerging data. In a report published by the EMA it was found that RWE studies are able to generate evidence in 56 days. [56] The studies were not always capable of generating evidence to answer research questions on rare diseases or specialist settings. However, half of the research questions were found to be achievable through the existing primary care data sources. In contrast a phase III clinical trial can take up to 4 years. [57]

Future outlook Europe

Between 2021-2023 the EMA has conducted a research and published a report alongside the European Medicines Regulatory Network (EMRN). [56] This report was mas meant to assess the possibility of enabling RWD/RWE use in regulatory decision making. It was concluded that currently RWE is used to support decision making in pharmacovigilance after a drug has been approved. However, RWE is rarely used in the initial phases of drug development. Currently the EMA and EMRN are bound on establishing a proper framework which will facilitate the use of RWE in every step of drug development, enabling RWE to support regulatory decision making. [56]

This led to a proposal to revise the general pharmaceutical legislation in Europe by the European Commission. Part of this proposal states that non-profit third parties are permitted conduct research on labels of approved drugs. This would expand the possibilities of extending labels of off-label drugs to include broader indications or populations. This could be an answer to decrease the prevalence of off-label prescribing. [58]

Study limitations

A limitation of our study is that the results on off-label prescribing in the Dutch pediatric population diagnosed with a high-grade CNS tumor were not statistically tested, therefore lacking a tested significance. A second limitation is the lack of information on dosage, outcome and adverse drug reactions in our dataset. Without this information the magnitude of problems off-label prescribing causes in the pediatric population remains unknown. The strength in this study is the large study population, that it includes patients over a period of 15 years and of diverse age groups.

The systematic literature review's limitation is the inclusion of only one database and that a sole reviewer conducted this review. The strength of the review lays in the inclusion and comparison of publications including both the EMA and FDA.

Conclusion

Off-label prescriptions occur frequently in Dutch pediatric high-grade CNS tumors with the prevalence increasing in follow-up line treatment. The last decade has seen an increase in the submission and acceptance of RWE in drug and extension of label applications. The EMA took note and has made a great effort in designing a framework and proposing a new pharmaceutical legislation to enable the use of RWE in extending existing labels. It is key to continue this trend of enabling and using RWE in regulatory decision making, one of the goals being a reduction in off-label prescribing.

Table 1.2: Demographic characteristics of the patient population treated in the follow-up line

	(a) Ependymomas and choroid plexus tumor	(b) and (d) Astrocytomas and other gliomas	(c) Intracranial and intraspinal embryonal tumors	(e) Other specified intracranial and intraspinal neoplasms	(f) Unspecified intracranial and intraspinal neoplasms	Overall
	(N=124)	(N=220)	(N=213)	(N=19)	(N=1)	(N=577)
Sex						
Male	61 (49.2%)	121 (55.0%)	155 (72.8%)	9 (47.4%)	1 (100%)	347 (60.1%)
Female	63 (50.8%)	99 (45.0%)	58 (27.2%)	10 (52.6%)	0 (0%)	230 (39.9%)
Age group						
0-3	59 (47.6%)	25 (11.4%)	68 (31.9%)	7 (36.8%)	1 (100%)	160 (27.7%)
4-9	38 (30.6%)	103 (46.8%)	98 (46.0%)	2 (10.5%)	0 (0%)	241 (41.8%)
10-14	20 (16.1%)	55 (25.0%)	31 (14.6%)	4 (21.1%)	0 (0%)	110 (19.1%)
15-17	7 (5.6%)	37 (16.8%)	16 (7.5%)	6 (31.6%)	0 (0%)	66 (11.4%)

Table 2: First line treatment of high-grade CNS tumors, nine most used drugs. Colored red if it was prescribed off-label and colored black if prescribed on-label.

			Vincristine	Cisplatin	Cyclophosphamide	Carboplatin	Etoposide	Lomustin	Temozolomide	Thiotepa	Doxorubicin	Iphospha
(a) ependymomas and choroid plexus tumors												
	0-3	(N=60)	28 (46.7%)	7 (11.7%)	18 (30.0%)	29 (48.3%)	21 (35.0%)			1 (1.7%)		
	4-9	(N=32)	5 (15.6%)	1 (3.1%)	3 (9.4%)	3 (9.4%)	1 (3.1%)	1 (3.1%)				
	10-14	(N=26)	2 (7.7%)	1 (3.8%)	1 (3.8%)	2 (7.7%)	2 (7.7%)	1 (3.8%)	1 (3.8%)			
	15-17	(N=9)	1 (11.1%)		1 (11.1%)		1 (11.1%)					
(b) and (d) Astrocytomas and other gliomas												
	0-3	(N=46)	5 (10.9%)	3 (6.5%)	3 (6.5%)	5 (10.9%)	2 (4.3%)	1 (2.2%)	4 (8.7%)			
	4-9	(N=155)	6 (3.9%)	4 (2.6%)	4 (2.6%)	8 (5.2%)	6 (3.9%)	2 (1.3%)	23 (14.8%)	3 (1.9%)	1 (0.6%)	
	10-14	(N=84)	4 (4.8%)		2 (2.4%)	3 (3.6%)	3 (3.6%)	3 (3.6%)	22 (26.2%)	1 (1.2%)		
	15-17	(N=42)	1 (2.4%)			1 (2.4%)			18 (42.9%)			
(c) Intracranial and intraspinal embryonal tumors												
	0-3	(N=104)	70 (67.3%)	43 (41.3%)	64 (61.5%)	65 (62.5%)	78 (75.0%)	6 (5.8%)	2 (1.9%)	22 (21.2%)	13 (12.5%)	11 (10.6%
	4-9	(N=143)	125 (87.4%)	115 (80.4%)	75 (52.4%)	44 (30.8%)	42 (29.4%)	68 (47.6%)	6 (4.2%)	9 (6.3%)	4 (2.8%)	5 (3.5%)
	10-14	(N=63)	50 (79.4%)	45 (71.4%)	25 (39.7%)	18 (28.6%)	18 (28.6%)	30 (47.6%)	11 (17.5%)	8 (12.7%)	1 (1.6%)	1 (1.6%)
	15-17	(N=21)	18 (85.7%)	16 (76.2%)	11 (52.4%)	4 (19.0%)	5 (23.8%)	9 (42.9%)	1 (4.8%)	1 (4.8%)		1 (4.8%)

(e) Other specified intracranial and intraspinal neoplasms												
	0-3	(N=9)	3 (33.3%)	3 (33.3%)	3 (33.3%)	5 (55.6%)	5 (55.6%)			1 (11.1%)		
	4-9	(N=4)	2 (50.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)	3 (75.0%)		1 (25.0%)	2 (50.0%)		
	10-14	(N=5)		1 (20.0%)	1 (20.0%)	2 (40.0%)	2 (40.0%)		2 (40.0%)	2 (40.0%)		
	15-17	(N=5)	1 (20.0%)		1 (20.0%)	4 (80.0%)	4 (80.0%)		3 (60.0%)	2 (40.0%)		
(f) Unspecified intracranial and intraspinal neoplasms												
	0-3	(N=1)	1 (100%)									1 (100%)
	4-9	(N=2)										
	10-14	(N=1)										

Table 3: Treatment after first line of high-grade CNS tumors, nine most used drugs. Colored red if it was prescribed off-label and colored black if prescribed on-label.

			Temozolomide	Etoposide	Cyclophosphamide	Vincristine	Carboplatin	Bevacizumab	Cytarabine	Thalidomide	Cisplatin	Lomustin
(a) ependymomas and choroid plexus tumors												
	0-3	(N=59)	6 (10.2%)	14 (23.7%)	6 (10.2%)	5 (8.5%)	4 (6.8%)		2 (3.4%)	1 (1.7%)	3 (5.1%)	
	4-9	(N=38)	2 (5.3%)	4 (10.5%)	1 (2.6%)					2 (5.3%)		
	10-14	(N=20)	3 (15.0%)	3 (15.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)		1 (5.0%)		
	15-17	(N=7)	1 (14.3%)	3 (42.9%)	1 (14.3%)					1 (14.3%)	2 (28.6%)	
(b) and (d) Astrocytomas and other gliomas												
	0-3	(N=25)	5 (20.0%)	1 (4.0%)	1 (4.0%)	2 (8.0%)	2 (8.0%)	1 (4.0%)			2 (8.0%)	
	4-9	(N=103)	33 (32.0%)	1 (1.0%)	2 (1.9%)	6 (5.8%)	5 (4.9%)	12 (11.7%)		1 (1.0%)	2 (1.9%)	1 (1.0%)
	10-14	(N=55)	18 (32.7%)		1 (1.8%)	1 (1.8%)		2 (3.6%)		1 (1.8%)		3 (5.5%)
	15-17	(N=37)	9 (24.3%)	2 (5.4%)		2 (5.4%)	1 (2.7%)	2 (5.4%)			1 (2.7%)	6 (16.2%)
(c) Intracranial and intraspinal embryonal tumors												
	0-3	(N=68)	11 (16.2%)	14 (20.6%)	6 (8.8%)	8 (11.8%)	3 (4.4%)	2 (2.9%)	4 (5.9%)	2 (2.9%)	3 (4.4%)	2 (2.9%)
	4-9	(N=98)	33 (33.7%)	32 (32.7%)	12 (12.2%)	4 (4.1%)	12 (12.2%)	9 (9.2%)	10 (10.2%)	8 (8.2%)	2 (2.0%)	3 (3.1%)
	10-14	(N=31)	10 (32.3%)	11 (35.5%)	4 (12.9%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	3 (9.7%)	1 (3.2%)	1 (3.2%)	

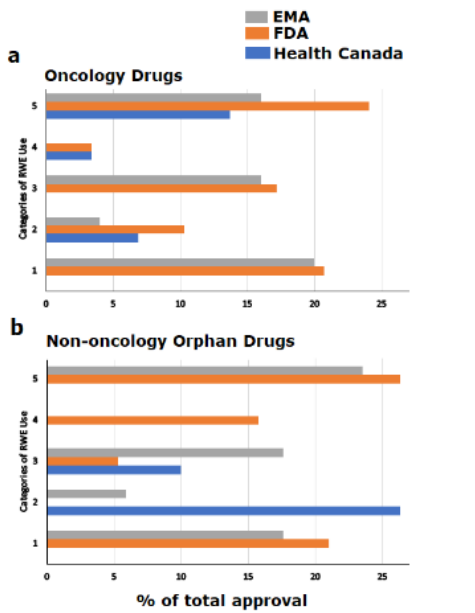
	15-17	(N=16)	3 (18.8%)	4 (25.0%)	1 (6.3%)	2 (12.5%)					2 (12.5%)	
(e) Other specified intracranial and intraspinal neoplasms												
	0-3	(N=7)	2 (28.6%)	4 (57.1%)	2 (28.6%)	2 (28.6%)	1 (14.3%)					
	4-9	(N=2)	1 (50.0%)									1 (50.0%)
	10-14	(N=4)		1 (25.0%)					1 (25.0%)			
	15-17	(N=6)	2 (33.3%)	2 (33.3%)		1 (16.7%)	1 (16.7%)		1 (16.7%)			
(f) Unspecified intracranial and intraspinal neoplasms												
	0-3	(N=1)										

Table 4: Summary of the included articles

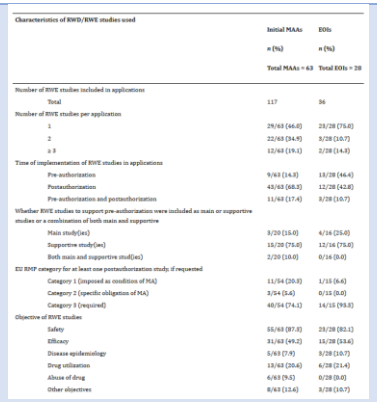
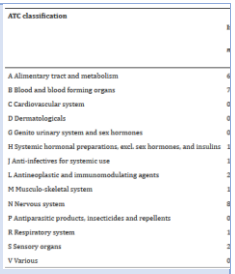
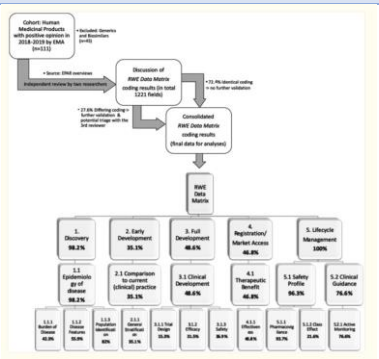
Author	Article	Regulatory agency	Initial/extension approval	Adults/children	Role RWD/RWE	Therapeutic area
Singh S et al. (2023) [59]	FDA approval summary: Alpelisib for PIK3CA-related overgrowth spectrum	FDA	Extension	Adults and children >2 years	EPIK-P1 is a single-arm trial conducted through an extended access program. The patients received alpesilib in a non-clinical trial setting. This provided real-world evidence to approve alpelisib.	Genetic disease
Bloomfield-Clagett B et al. (2023) [34]	Use of real-world evidence in neuroscience-related new drug and biologics applications for novel therapeutics	FDA	Initial approval	Onasemnogene abeparvovec children <2 years Risdiplam adults and children Viltolarsen adults and children	-This review included 30 new drug approvals and biologics license applications of which 3(10%) included RWE from 2019-2021. -For each application RWD was used as a comparator arm. -Onasemnogene abeparvovec used an RWE study to provide primary evidence on efficacy -Risdiplam RWD provided supportive evidence for approval -Viltolarsen was approved through an RCT with RWD analyses being unreliable	Neurology
Ro SK et al. (2023) [43]	Statistical considerations on the use of RWD/RWE for oncology drug approvals: overview and lessons learned	FDA and EMA	Initial and extension	Adults and children	-Selinexor RWD external control to single arm study/supportive evidence/ initial/ issues: selection bias/ outcome: not able to demonstrate comparative efficacy -Tafasitamib compare tafa/len single arm to RWD len monotherapy to isolate tafa benefit/ supportive/ initial/ issues: small sample size, missing data/ outcome: not able to demonstrate comparative efficacy -Blincyto comparing single arm blincyto to historical control to demonstrate no harm/ supportive/ revision initial/ outcome unknown	Oncology

					-Erdafatinib comparing Erda to RWD PD-L1/PD-1 data/ supportive/ initial/ issues: small sample size, missing data/ unknown outcome -Pembro/Lenvatinib compare single arm pem/len to historical studies mono pem or len to isolate drug effect/ supportive/ extension/ outcome: demonstrated added benefit combination therapy -Various PD-L1/PD-1 drug combo, comparing each drug monotherapy efficacy to sunitinib to isolate their contribution in the combo drug efficacy/ supportive/ extension/ outcome: demonstrated evidence for added benefit each drug in combotherapy	
Bakker E et al. (2023) [35]	Contribution of real-world evidence in European Medicines Agency's regulatory decision making	EMA	Initial and extension	Adults and children	Of 158 MAAs 32 contained references to RWD/RWE and of 158 EoIs 14 contained references to RWD/RWE. RWD/RWE was used to generate evidence on efficacy. -8 MAAs submitted RWE as main evidence pre-authorization. 4 were authorized, in 3 approvals RWE was used in the decision. -8 MAAs submitted RWE as supportive evidence pre-authorization, 3 were authorized in, 1 approval RWE was used in the decision. RWE: external comparators, safety/efficacy contextualization or data collection -5 EoIs submitted RWE as main evidence pre authorization. 3 were authorized, in 2 approvals RWE was used in the decision. -5 EoIs submitted RWE as supportive evidence pre-authorization. 5 were authorized, in 3 approvals RWE was used in the decision. RWE: external comparators, safety/efficacy contextualization or data collection	

Serrano P et al. (2022) [60]	Real-world data in drug development strategies for orphan drugs: Tafasitamab in B-cell lymphoma, a case study for an approval based on a single-arm combination trial	EMA and FDA	Initial	Adults	''The use of RWD had been incorporated prospectively in the clinical development and drug approval strategy''. This study discusses a comparison between monotherapy lenalidomide and combination therapy tafasitamab+lenalidomide to investigate the efficacy of tafasitamab in the combination. The monotherapy cohort was a historical comparator using RWD. The combination was approved by the EMA and FDA because of the comparison made with RWD	Hematology
Jandhyala R et al. (2022) [36]	The effect of adding real-world evidence to regulatory submissions on the breadth of population indicated for rare disease medicine treatment by the European Medicines Agency	EMA	NA	NA	100 engagements with 87 only containing RCT data and 13 containing both RWE and RCT. approvals including RWE more often had a broader population indication. 76.92% compared to 56.32% however, this was not significant. It was estimated that within 17 years (linear rise) or 13 years (exponential rise) a power of 80% to detect a 20% difference between RCT and RWE would be achievable.	NA

Lau C et al. (2022) [33]	Health Canada usage of real-world evidence (RWE) in regulatory decision making compared with FDA/EMA usage based on publicly available information	Health Canada, FDA and EMA	NA	NA	 Keys: 1. Review and use of retrospective/prospective Real Word studies and use of historical control for patient population/endpoint comparisons. 2. Review and use of retrospective/prospective Real Word studies for efficacy/safety comparison 3. Review and use of historical data for efficacy/safety comparison 4. Mention of the review of RWE – inconclusive whether it was used for decision making 5. Mention of the review of historical data – inconclusive whether it was used for decision making Canada: 29 and 21 approvals oncology/non-oncology FDA: 29 and 19 approvals oncology/non-oncology EMA: 25 and 17 approvals oncology/non-oncology Figure shows how much each agency used RWE in their decision making.	Oncology Non-oncology
Purpura CA et al. (2022) [29]	The role of real-world evidence in FDA-approved new	FDA	Initial	Adults and children	-FDA approved 378 NDAs and BLAs -136 approvals of interest	-Oncology, 30 approvals

	drug and biologics license applications				-116 included RWE (83 support therapeutic context and 88 support safety and/or efficacy) - of the 88 studies including RWE for safety/efficacy, 8 studies included RWE of substantial or primary evidence, 57 supportive evidence, 13 RWE not adequate, 10 not addressed -of the 88 approvals with RWE, 43 supported safety, 15 efficacy and 30 both safety/efficacy	-Neuroscience, 13 approvals -Infectious diseases 16 approvals -Endocrinology and metabolism, 8 approvals -Radiology, 6 approvals -Hematology, 2 approvals -Dermatology, 2 approvals -Gastroenterology, 2 approvals -Allergy, 1 -Anesthiology, 1 -Cardiovascular, 2 -Gynecology, 1 -Urology, 1 -Autoimmune, 1 -Cosmetic, 1 -Respiratory, 1

Flynn R et al. ((2022) [30]	Marketing authorization applications made to the European Medicines Agency in 2018-2019: What was the contribution of real-world evidence?	EMA	Initial and extension	63 MAAs with RWE total 22 pediatric 28 EoIs RWE 15 pediatric	 RWE used in ~40% of MAAs (mainly postauthorization) and ~18% of EoIs(balance pre- and post-authorization). Surprising since it would be assumed that if applying for an EoI RWE would already have been generated. However, the study does not discuss in how big of an impact or what precise role RWE had in the decision making.	
Eskola SM et al. (2022) [31]	Use of real-world data and evidence in drug development of medicinal products centrally authorized in Europe in 2018-2019	EMA	Initial	NA	 -111 medicinal products were evaluated above shows the RWE signature in different stages of development/authorization	-Oncology -Infectious diseases -Nervous system disorders -Alimentary tract and metabolism disorders -Blood -Respiratory system -Musculoskeletal system -Sensory organs

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>-77.5% of products required postapproval monitoring
-23.4% were orphan medicines
-8.1% were approved conditionally</td><td>-Cardiovascular system
-Genito-urinary and sex hormones
-Systemic hormonal preparations</td></tr>
<tr><td>Arondekar B et al. (2022) [41]</td><td>Real-world evidence in support of oncology product registration: a systematic review of new drug application and biologics license application approvals from 2015-2020</td><td>FDA</td><td>Initial</td><td></td><td>-Between 2015-2020 133 NDA and BLA approvals in oncology
-11 included RWE to support efficacy
-Another 2 supplemental NDA and BLA that included RWE for efficacy
-Average time to approval was 5.7 years
<table>
<tr><th>Drug</th><th>Population</th><th>RWE purpose</th><th>RWE us in decis</th></tr>
<tr><td>Avelumab</td><td>Adults and children older than 12 years</td><td>Contextualization</td><td>Yes</td></tr>
<tr><td>Axicabtagene ciloleucel</td><td>Adults</td><td>Contextualization</td><td>Yes</td></tr>
<tr><td>Blinatumomab</td><td>Adults</td><td>Contextualization and comparison</td><td>Yes</td></tr>
<tr><td>Entrectinib</td><td>Adults</td><td>Comparison</td><td>No</td></tr>
<tr><td>Erdafitinib</td><td>Adults</td><td>Contextualization and comparison</td><td>No</td></tr>
<tr><td>Palbociclib</td><td>Adults</td><td>Contextualization</td><td>Yes</td></tr>
<tr><td>Polatuzumab vedotin-piiq</td><td>Adults</td><td>Contextualization</td><td>No</td></tr>
<tr><td>Selinexor</td><td>Adults</td><td>Comparison</td><td>No</td></tr>
<tr><td>Avapritinib</td><td>Adults</td><td>Contextualization</td><td>Yes</td></tr>
</table></td><td></td></tr>
</table>

					<table><tr><td>Capmatinib</td><td>Adults</td><td>Contextualization</td><td>Yes</td></tr><tr><td>Tafasitamab</td><td>Adults</td><td>Comparison</td><td>Yes</td></tr><tr><td>Tazemetostat (NDA 211723)</td><td>Adults and children >16 years</td><td>Contextualization</td><td>No</td></tr><tr><td>Tazemetostat (NDA 213400)</td><td>Adults</td><td>Contextualization</td><td>No</td></tr></table>	
Mahendraratnam N et al. (2022) [28]	Understanding use of real-world data and real-world evidence to support regulatory decisions on medical product effectiveness	FDA	Initial and extension	Adults and children	<table><tr><td></td><td colspan="4">Medical products (n = 34)</td></tr><tr><td></td><td>Oncology n (%)</td><td>Hematology n (%)</td><td>Neurology n (%)</td><td>Oth n (%)</td></tr><tr><td>Number of submissions</td><td>9 (26)</td><td>6 (18)</td><td>4 (12)</td><td>15 (</td></tr><tr><td>Approval type</td><td></td><td></td><td></td><td></td></tr><tr><td>Original approval</td><td>7 (78)</td><td>5 (83)</td><td>4 (100)</td><td>12 (</td></tr><tr><td>Labeling change</td><td>1 (11)</td><td>1 (17)</td><td>0 (0)</td><td>2 (1</td></tr><tr><td>Original approval and labeling change</td><td>1 (11)</td><td>0 (0)</td><td>0 (0)</td><td>1 (</td></tr><tr><td>Designation</td><td></td><td></td><td></td><td></td></tr><tr><td>Orphan designation</td><td>7 (78)</td><td>6 (100)</td><td>4 (100)</td><td>11 (</td></tr><tr><td>Indicated for pediatric use</td><td>2 (22)</td><td>4 (67)</td><td>4 (100)</td><td>9 (6</td></tr><tr><td>Indicated for use in rare diseases</td><td>5 (56)</td><td>5 (83)</td><td>4 (100)</td><td>4 (2</td></tr></table><table><tr><td></td><td>RWE included in label[b] n (%)</td><td>RWE not included in label[c] n (%)[e]</td><td>Unkno n (%</td></tr><tr><td>Number of submissions</td><td>20 (59)</td><td>12 (35)</td><td>2 (6</td></tr><tr><td>Study design</td><td></td><td></td><td></td></tr><tr><td>Randomized</td><td>2 (10)</td><td>0 (0)</td><td>1 (5</td></tr><tr><td>External control/Benchmark</td><td>8 (40)</td><td>10 (83)</td><td>0 (0</td></tr><tr><td>Cohort</td><td>1 (5)</td><td>1 (8)</td><td>0 (0</td></tr><tr><td>Case series</td><td>8 (40)</td><td>0 (0)</td><td>1 (5</td></tr><tr><td>Natural history</td><td>1 (5)</td><td>1 (8)</td><td>0 (0</td></tr></table> -From 1954 to 2020 34 cases where RWE was submitted as evidence for efficacy.	
Gross AM et al. (2021) [61]	Using real-world data to support regulatory approval of drugs in rare diseases: a review of opportunities, limitations & a case example	FDA	Initial	Adults and children	-Selumetinib was approved for treating Neurofibromatosis type 1 -It was a single arm phase II trial -This was compared to an age-matched cohort of an ongoing NF1 natural history study -It was also compared to a ''failed'' trial for tipifarnib, providing another retrospective cohort	Oncology
De S et al. (2021) [38]	Leveraging real-world evidence: a paradigm shift in regulation	FDA and EMA	Initial	Children	-Both the FDA and EMA approved Brineura in 2017 for the treatment of Batten disease.	Genetics

					The clinical trial that established efficacy was nonrandomized, single-arm dose escalation in 22 children. -This was compared to a historical cohort of 42 untreated patients with CLN2 disease.	
Feinberg BA et al. (2020) [42]	Use of real-world evidence to support FDA approval of oncology drugs	FDA			-Case study 1, single-arm, open label, phase 2 study 88 patients treated with avelumab for MCC. RWE component was a historical control which contained data on 14 patients who were treated with chemotherapy for MCC. Objective response rate (ORR) and duration of response (DOR) were compared. FDA found limitations in small sample size and selection bias. Data was only used exploratory and to further characterize risk/benefit avelumab. Accelerated approval with post-marketing requirement (PMR) to conduct a clinical trial. -Case 2, randomized, open label, active-controlled neuroendocrine tumors therapy trial, to evaluate safety/efficacy lutetium lu177 dotatate plus octreotide vs. octreotide in the treatment of *progressive, well-differentiated, locally advanced/inoperable or metastatic SSTR-positive midgut carcinoid tumors*. RWE component comprised of an open label, single-arm, expanded access study of 360 patients with SSTR-positive GEP-NET. ORR and DOR were compared. FDA noted differences in tumor types, eligibility criteria, dosing, timing of response and safety assessments. It was approved, but for treatment of SSTR-positive GEP-NET, which is narrower than initial indication -Case 3, open label, single-arm BLAST-study investigated efficacy blinatumomab for the treatment of MRD-positive B-cell precursor ALL. RWE component was a historical comparison group. 73 patients from BLAST were compared to 182 historic controls to	Oncology

					compare relapse free survival. Limitations: small sample size, different lengths follow-up and potentially different treatment patterns. Accelerated approval, however a PMR was a confirmatory RCT. -Case 4, no clinical trials were conducted for Palbociclib. A supplemental NDA was proposed to broaden indication for Palbociclib to include male patients and a retrospective outcome analysis. RWE components was 12 patients treated with Palbociclib being compared to 16 patients treated with other drugs with the endpoint being tumor response. The other RWE component was a comparison of 34 patients on Palbociclib + aromatase inhibitor/fulvestrant vs. 214 patients on aromatase/fulvestrant. Palbociclib showed a longer prescription order duration (survival?). RWE on safety included HER data on 25 male patients, 362 post marketing safety reports and 2 phase I studies. -Case 5, open label, single-arm study to evaluate safety/efficacy selinexor in refractory myeloma. Primary endpoint ORR. DOR and OS secondary endpoints. RWE component was retrospective observational study using HER data to compare OS between the two. FDA found methodological flaws in the comparison and it could not be used in the decision making. Approval was later granted because of an ongoing phase III trial.	
Wu J et al. (2020) [37]	Use of real-world evidence in regulatory decisions for rare diseases in the United States - current status and future directions	FDA	Initial	Adults and children	-Case 1, Efficacy of cerliponase alfa (brineura) in nonrandomized, single-arm, open label, dose escalation study in 24 pediatric patients with CLN2 disease. Historic cohort of 42 untreated CLN2 patients was the comparison group. Efficacy conclusions were based on best matched patients and accounted for confounders. 17 pairs were analyzed and the outcome supported the approval.	Neuroscience Genetics

					-Case 2, Asfotase alfa was approved based on two multicenter, multinational, single-arm, open label, phase 2 intervention studies in 68 treated patients compared with 48 patients for HPP. OS were compared with an OS of 91.2% in treated patients vs 27.1% in historical control group. -Case 3, Uridine triacetate for treatment of hereditary oroticaciduria (HOA) (extremely rare, 20 cases since 1959) approval uridine triacetate based on single arm trial with 4 patients and literature review of 19 individuals treated with uridine. Small trial and RWE literature enough for approval.	
Baumfeld Andre E et al. (2020) [39]	Trial designs using real-world data: the changing landscape of the regulatory approval access	FDA and EMA	Initial and extension		-Case 1, avelumab approved for treating MCC by FDA and EMA. Historical controls used as RWE. -Case 2, blinatumomab approved for treating relapsed/refractory Philadelphia chromosome-negative acute lymphoblastic leukemia by FDA and EMA. Single-arm phase 2 study compared to historical controls. -Case 3, paliperidone palmitate label extension to include treatment of schizophrenia, based on open-label pragmatic trial. Trial was conducted in real world clinical practice. First example of the use of RWE from pragmatic trial to support a regulatory decision.	See table, for indications
Bolislis WR et al. (2020) [32]	Use of real-world data for new drug applications and line extensions	FDA and EMA	Initial and extension	Adults and children	-In NDAs RWD was typically comparative data as a (historical) control group for safety/efficacy. (e.g., cerliponase alfa, cholic acid [FDA approval], tisagenlecleucel, strimvelis, nusinersen, Zalmoxis)	multiple

					-In other forms RWD was used to characterize biomarkers and disease manifestations to enable identification of patient population for the study. (e.g., alipogene tiparvovec, elosulfase alfa, avelumab) -RWD in line extensions included cases in a new indication (blinatumomab and paliperidone palmitate) -RWD in completing labeling by assessing safety/efficacy during pregnancy (fosamprenavir) -RWD on tolerability (etravirine) -RWD on dosage and administration (nusinersen) -RWD to expand the use to include a broader population (alglucosidase alfa, children <8 years), (eculizumab, children), (etravirine, children and pregnant women) and (palbociclib, adult men)	
Raphael MJ et al. (2020) [40]	Real-world evidence and regulatory drug approval	FDA	Initial and extension	Adults	-Blinatumomab, avelumab and Palbociclib -Same cases as described before	

Table 5: Key information of 12 of 19 publications on initial or label extension approval of the included articles

Article	Agency	Label	Drug	Population	Role	Evidence	What
Singh et al. (2023) [59]	FDA	Extension	Alpelisib	Adults and children >2	Retrospective chart review of patients who received aleplisib to show efficacy in PROS	Primary	Safety/efficacy
Bloomfield-Clagett et al. (2023) [34]	FDA	Initial	Onasemnogene	Adults and children	External control	Primary	Efficacy
	FDA	Initial	Risdiplam	Adults and children	External control	Supportive	Efficacy
	FDA	Initial	Viltolarsen	Adults and children	External control	Supportive (unreliable)	Efficacy
Ro et al. (2023) [43]	FDA and EMA	Initial	Selinexor	Adults	External control	Supportive (not used)	Efficacy
	FDA and EMA	Initial	Tafasitamab	Adults	External control	Supportive (not used)	Efficacy
	FDA and EMA	Initial	Blincyto	Adults and children	External control	Supportive	Safety
	FDA and EMA	Initial	Erdafitinib	Adults	External control	Supportive	Efficacy
	FDA and EMA	Extension	Pembro/lenvatinib	-	External control	Supportive	Efficacy (each drug)
	FDA and EMA	Extension	PD-L1/PD1 drug	-	External control	Supportive	Efficacy (each drug)
	FDA and EMA	Initial	Yescarta	Adults	External control	Supportive	Efficacy
	FDA and EMA	Initial	Kymriah	Adults	External control	supportive	Efficacy
Bakker et al. (2023) [35]	EMA	Initial	Onasmenogene	Adults and children	External control, data collection, contextualization (research database)	Primary	Safety/efficacy

	EMA	Initial	Iva-, teza- and elexacaftor	Adults and children(>12)	Efficacy data collection (registry)	Primary (not used)	Efficacy
	EMA	Initial	Trientine dihydrochloride	Adults and children (>5)	Safety/efficacy data collection (EHR and literature)	Primary and supportive	Safety/efficacy
	EMA	Initial	Melphalan	Adults and children	Efficacy data collection (literature)	Primary and supportive	Efficacy
	EMA	Extension	Ravulizumab	Adults and children	Efficacy contextualization (registry)	Supportive (unknown)	Efficacy
	EMA	Extension	Cholera vaccin, oral, live	Adults and children (>6)	Efficacy data collection (literature)	Supportive (unknown)	Efficacy
	EMA	Extension	Hydroxycarbamide	Adults and children (>2)	Safety/efficacy data collection (literature)	Supportive	Safety/efficacy
Serrano et al. (2022) [60]	FDA and EMA	Initial	Tafasitamab	Adults	External control (mono lenalidomide) compared to combination therapy to investigate efficacy tafasitamab	Primary	Efficacy
Arondekar et al. (2022) [41]	FDA	Initial	Avelumab	Adults and children older than 12 years	External control, (Contextualization)	-	-
	FDA	Initial	Axicabtagene ciloleucel	Adults	Contextualization	-	-
	FDA	Initial	Blinatumomab	Adults	Contextualization and External control	-	-
	FDA	Initial	Entrectinib	Adults	Comparison	-	-
	FDA	Initial	Erdafitinib	Adults	Contextualization and External control	-	-
	FDA	Extension	Palbociclib	Adults	Contextualization	-	-

	FDA	Initial	Polatuzumab vedotin-piiq	Adults	Contextualization	-	-
	FDA	Initial	Selinexor	Adults	External control	-	-
	FDA	Initial	Avapritinib	Adults	Contextualization	-	-
	FDA	Initial	Capmatinib	Adults	Contextualization	-	-
	FDA	Initial	Tafasitamab	Adults	External control	-	-
	FDA	Initial	Tazemetostat(NDA 211723)	Adults and children >16 years	Contextualization	-	-
	FDA	Initial	Tazemetostat(NDA 213400)	Adults	Contextualization	-	-
Gross et al. (2021) [61]	FDA	Initial	Selumetinib	Adults and children	External control	Primary	Safety/efficacy
De et al. (2021) [38]	FDA and EMA	Initial	Cerliponase alfa	Children	External control	Primary	Efficacy
Feinberg et al. (2020) [42]	FDA	Initial	Avelumab	Adults	External control	Supportive (not used)	Efficacy
	FDA	Initial	Lutetium	Adults	Retrospective expanded access study	Supportive	Safety/efficacy
	FDA	Extension	Blinatumomab	Adults	External control	Supporting	Efficacy
	FDA	Extension	Palbociclib	Adults	Retrospective outcome analysis	Supporting	Safety
	FDA	Initial	Selinexor	Adults	Retrospective observational study (external comparator)	Supportive (not used)	Safety/efficacy
Wu et al. (2020) [37]	FDA	Initial	Cerliponase alfa	Children	External control	Primary	Efficacy
	FDA	Initial	Asfotase alfa	Children	External control	Primary	Efficacy

	FDA	Initial	Uridine triacetate	Children	Retrospective literature review/case study	Primary	Efficacy
Baumfeld et al. (2020) [39]	FDA	Initial	Aglucosidase alfa	Adults and children	Placebo RCT supported by clinical outcomes from a registry and external control	Supportive	Efficacy
	FDA	Initial	Carglumic acid	Adults and children	Retrospective review, patients treated with carglumic acid	Primary	-
	FDA	Initial	Glucarpidase	Adults and children	Open-label nonrandom compassionate use protocol	Supportive	Efficacy
	FDA	Initial	Coagulation factor VIIa	Adults and children	Approval based on retrospective evidence collected from 2 registries	Primary	-
	FDA and EMA	Initial	Blinatumomab	Adults and children	External control	Supporting	Safety/Efficacy
	FDA	Initial	Cholic acid	Adults and children	Retrospective case report from chart review of open label SAT and retrospective literature review to form external control	Primary	-
	FDA	Initial	Uridine tracetate	Adults and children	Open-label safety and efficacy trial, Historical case reports as comparison	-	Safety/efficacy
	FDA	Initial	Methylene blue	Adults and children	Retrospective case reports and literature review	-	-
	EMA	Initial	Allogenic t cells	Adults	External control group collected from a registry	-	-(WITHDRAWN EMA)
	FDA	Initial	Eteplirsen	Adults	External control matched to treatment arm and compared	-	-

	FDA	Extension	Ivacaftor	Adults and children	Extension based on post-marketing registry data	-	-
	EMA	Extension	Eculizumab	Adults and children	Post-approval registry data	-	Safety/efficacy
	FDA and EMA	Initial	Cerliponase alfa	Children	External control	Primary	Efficacy
	FDA and EMA	Initial	Axicabtagene ciloleucel	Adults	External control	Primary	Efficacy
	FDA	Extension	Thiotepa	Children	Retrospective study of pediatric patients	Primary	-
	FDA	Initial	Migalastat	Children	New RCTS and RWE from use of migalastat in EU	-	-
	FDA	Initial	Lutetium dotatate	Adults	External control	-	Efficacy
	FDA	Initial	Fish oil triglycerides	Adults and children	Two SATs matched with external controls	-	-
	FDA and EMA	Extension	Blinatumomab	Adults	SAT supported with RWE	-	-
	FDA	Extension	Palbociclib	(male) adults	Retrospective safety analysis	-	Safety
Raphael et al. (2020) [40]	FDA	Initial	Blinatumomab	Adults and children	External control	Supporting	Efficacy
	FDA	Initial	Avelumab	Adults	External control	Supporting (not used)	Efficacy
	FDA	Extension	Palbociclib	Adults	Retrospective safety analysis	Supporting	Safety

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Appendix1. Search string for the systematic literature review (part 2 of the study)

(((real world data[Title/Abstract]) OR (real world evidence[Title/Abstract]) OR (observational data[Title/Abstract]))) AND ((((FDA[Title/Abstract]) OR (food and drug administration[Title/Abstract]) OR (EMA[Title/Abstract]) OR (european medicines agency[Title/Abstract]) OR (ICH[Title/Abstract]) OR (international council for harmonisation[Title/Abstract]))) OR (drug approval[MeSH Terms]))

Appendix 2. Role of RWE publication by Baumfeld Andre E et al. (2023) [39]

Drug	Indication (Health Authority, Year)	RWE Use Examples
Lumizyme/Myozyme (alglucosidase alfa)	Pompe Disease (FDA, 2010)	The approval relied on a placebo-controlled trial, in late-onset Pompe disease, supported by clinical outcomes data in infantile-onset patients from the Pompe Registry, which was launched as a post-marketing commitment for the 2006 Myozyme approval in Europe. The registry data showed increased survival at 18 months in Lumizyme patients compared with age- and disease-matched historical controls. The Myozyme approval also relied on a comparison to a 61-patient historical control group.56
Carbaglu (carglumic acid) tablets	Hyperammonia caused by N-acetylglutamate (NAGS) deficiency (FDA, 2010)	The approval relied on a retrospective review of 23 NAGS deficiency patients who received Carbaglu for a median of approximately eight years, and on data from 3 patients with NAGS deficiency treated in a prospective trial.59
Voraxaze (glucarpidase)	Toxic plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function (FDA, 2012)	The chemotherapy toxicity reversal agent approval was supported by clinical evidence from 22 patients in two efficacy studies, including an open-label non-randomized compassionate use protocol.56, 60, 61, 62
NovoSeven (Coagulation Factor VIIa)	Glanzmann's thrombasthenia with refractoriness to platelet transfusions (Treatment of bleeding episodes and the peri-operative management) (FDA, 2014)	The approval was based upon evidence collected from the global Glanzmann's Thrombasthenia Registry (218 patients with 1,073 bleeding and surgical events) and the Hemostasis & Thrombosis Research Society Registry (7 patients with 23 bleeding episodes).63
Blincyto (blinatumomab)	Philadelphia chromosome-negative (Ph -) relapsed or refractory positive B-cell precursor acute lymphoblastic leukemia (ALL) (FDA 2014, EMA 2015)	The main study supporting this accelerated approval was a Phase 2, multicenter, open-label, single-arm trial that included a core study of 185 patients to assess the treatment efficacy and safety. The results of this study were compared to a retrospective pooled analysis of historical data on 1139 patients from 1990 to 2014 on hematological remission rates and survival among adult patients with relapsed/refractory ALL treated with standard of care therapy. This historical database was assembled by combining existing databases from the USA and European Union from 1139 patients that had similar characteristics to the patients in the main study with respect to previous treatment status.16, 64, 65, 66
Cholbam (cholic acid)	Bile acid synthesis disorders (FDA, 2015)	The approval was based on a retrospectively devised case report form from chart review of patients in the open-label, single-arm expanded access protocol and a retrospective literature review to construct a historical control.56
Vistogard (Uridine triacetate)	Emergency treatment of certain types of chemotherapy overdose (FDA, 2015)	Vistogard was approved as an emergency treatment for patients who receive overdoses of two chemotherapy drugs or exhibit severe adverse reactions to the drugs following open-label safety and efficacy trials of 135 patients. The patient had either received overdoses of fluorouracil or capecitabine or presented with severe or life-threatening toxicities within
ProVay Blue (methylene blue)	Acquired methemoglobinemia (FDA, 2016)	The ProVay Blue accelerated approval was based on retrospective case reports found in a multicenter chart review along with cases found in literature search. Like many of the orphan products approved with RWE, ProVay Blue used the 505(b)(2) NDA pathway, which allows for data not developed by the sponsor to be incorporated in the application.56, 68, 69, 70, 71
Zalmoxis (allogeneic T cells)	Hematopoietic stem cell transplantation with high-risk hematological malignancies (EMA, 2016)	For this approval, a control group was collected from the European transplant registry based on the same criteria used in the control group of an ongoing Phase III trial and a specific sets of matching parameters.72, 73, 74
Exondys (eteplirsen)	Duchenne muscular dystrophy (FDA 2016)	The Accelerated approval was based on matching and comparison of eteplirsen arm with historic control arm from the Italian DMD Registry database.75
Kalydeco (ivacaftor)	10 cystic fibrosis (CF) mutations to 33 (FDA, 2017)	The label expansion was based on post-marketing registry data and mechanistic information from lab studies.56
Soliris (eculizumab)	Paroxysmal nocturnal hemoglobinuria where evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (EMA, 2017)	Soliris was initially restricted to use in patients with a certain disease severity. The expanded indication was based on disease registry data to help demonstrate effectiveness. The registry was established at the time of authorization of Soliris with the twin aims of evaluating the safety of Soliris and also characterizing disease progression, clinical outcomes, morbidity, and mortality. The registry included data from both Soliris treated and untreated patients.74, 76, 77
Brineura (cerliponase alfa)	Batten disease (EMA and FDA 2017)	The FDA approved Brineura as a treatment for a form of Batten disease, following a single-arm study which used a natural history control. Brineura was the first FDA-approved treatment to slow loss of walking ability in patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2). The clinical trial establishing Brineura's efficacy was a non-randomized, single-arm dose escalation clinical study in 22 symptomatic pediatric patients. The control or comparator consisted of 42 untreated patients with CLN2 disease from a natural history cohort.56, 58, 78, 79, 80, 81, 82
Bavencio (avelumab)	Metastatic Merkel cell carcinoma (FDA and EMA 2017)	Accelerated approval based on a single-arm, open-label study compared with historical control from electronic health records.15, 83
Yescarta (Axicabtagene Ciloleucel)	Diffuse large B-cell lymphoma (FDA 2017 and EMA 2018)	The full approval was granted for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy based on the findings of the single-arm ZUMA-1 study which compared the treatment response with historical controls from scientific literature.84, 85

Tepadina (thiotepa)	Reduce the risk of rejection in pediatric call 3 beta-thalassemia (FDA, 2017)	The label expansion was based on a retrospective study of pediatric patients with class 3 beta-thalassemia who underwent allogeneic hematopoietic stem cell transplantation.
Galafold (migalastat)	Fabry disease (FDA 2018 and EMA 2016)	This was an accelerated approval by the FDA. The data included new cardiac and renal data from clinical trials, data from long-term extension studies and real-world data from the commercial launch of migalastat in Europe, particularly on patients transitioning from existing enzyme replacement therapy. The sponsor also provided patient perspectives to FDA on the unmet need in Fabry and the lack of treatment options in the US.[86, 87, 88, 89, 90]
Lutathera (lutetium Lu 177 dotatate)	Gastroentereopancreatic neuroendocrine tumors (FDA, 2018)	The FDA approved Lutathera, a radioactive drug for treatment of somastatin receptor-positive instances of a type of cancer that affects the pancreas or gastrointestinal tract known as gastroenteropancreatic neuroendocrine tumors (GEP-NETs), based in part on data generated through the expanded access program. Lutathera's approval was supported by two studies. One was a RCT with 229 patients. The second study was based on data from a single-arm, open-label study of 1,214 patients with somatostatin receptor-positive tumors, including GEP-NETS, who received Lutathera at a single site in the Netherlands.[58, 62, 91, 92, 93]
INVEGA SUSTENNA (paliperidone palmitate)	Treatment of schizophrenia in adults and treatment of schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants (FDA, 2018)	The label expansion for this long-acting form of INVEGA was based on the Paliperidone Palmitate Research In Demonstrating Effectiveness (PRIDE) study a prospective, open-label, randomized, 15-month pragmatic study comparing the long-acting form with oral antipsychotic medications in patients with schizophrenia who have a history of contact with the criminal justice system.[19, 20, 21]
Omegaven (fish oil triglycerides)	Parenteral nutrition-associated cholestatis (PNAC) (FDA, 2019)	The approval was based on two single-arm trials, matched to historical control arm from hospital records.[94, 95]
Blincyto (blinatumomab)	B-cell precursor acute lymphoblastic leukemia in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% (FDA 2018 and EMA 2019)	The label expansion was based on the results of a single-arm trial supported by RWE to include indication for patients with minimal residual disease in which cancer cells are present at a low level that cannot be detected microscopically.[17, 18, 22, 96]
Ibrance (Palbociclib)	HR+, HER2- advanced/metastatic breast cancer (FDA, 2019)	The label was expanded to include treatment in males based on post-marketing reports and electronic health records as part of the totality of evidence. Real-world data from electronic health records showed encouraging response rates with Ibrance, a CDK4/6 inhibitor in combination with an aromatase inhibitor or fulvestrant in the male patient population. The safety profile of Ibrance in male patients was consistent with the tolerability in female patients who were treated with palbociclib, according to the data.[102]