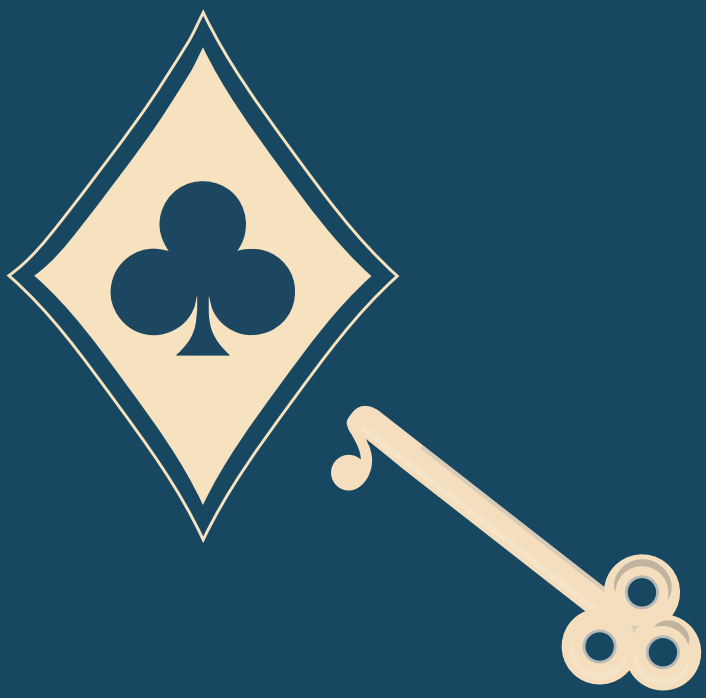
UNLOCKING THE VALUE OF EXPANDED ACCESS

Ethical, Statistical, and Policy Considerations



TOBIAS BOY POLAK

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Unlocking the Value of Expanded Access
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De waarde van 'expanded access'
verhandelingen over ethiek, statistiek en beleid

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Promotor:	Prof.dr. C.A. Uyl – de Groot
Overige leden:	Prof.dr.ir. H. Boersma Dr. E. Bunnik Prof.dr. A. Caplan
Copromotor:	Dr. J. van Rosmalen

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PRELUDE

INTRODUCTION

To ensure patients and physicians have access to safe and effective drugs, regulators require the conduct of clinical trials to identify the risks and benefits of new treatments.[1] The process of drug development requires effort and time, and as many as 15 years may pass to complete all phases of drug development.[2] This encompasses preliminary pre-clinical research in petri dishes, followed by phase I trials involving healthy volunteers to evaluate safety and establish tolerable dosage levels. Next, in phase II, the investigational drug is tested on a larger group of patients with the targeted condition to determine its effectiveness, optimal dosage, and any further side effects. Finally, phase III trials test the drug on a large group of patients to compare the effectiveness and safety of the new drug or therapy with existing treatments or placebos.

Despite remarkable advances in medicine for some disease areas, a substantial patient population remains without treatment options. Patients with mild, slowly progressing, non-lethal diseases may have the luxury of time at their disposal to await the outcomes of clinical trials to develop safe and effective medicine. Patients with life-threatening or seriously debilitating conditions cannot afford to await the results of regulatory evaluation and have sought access to investigational medicine through 'expanded access' pathways.[3,4]

The expanded access pathway provides a means to access investigational medicine when access through the preferred route - trial participation - is not possible. While patients may individually benefit from participating, clinical trials primarily generate knowledge for the collective advancement of medical science. However, a variety of barriers exist that impede patients from participating in trials, including ineligibility due to medical factors such as frailty, the presence of comorbidities, or the use of concomitant medications.[5] Practical barriers, such as limited awareness of trials among patients and physicians, challenges with scheduling and travel to trial sites, or a complete lack of trials further hinder patient enrollment.[6] Regrettably, research strongly suggests that sexist and racist factors worryingly hinder patient participation.[7] When approved options are inadequate and trial participation is not feasible, patients in dire need may seek to access investigational drugs through legislated expanded access pathways.

The history of expanded access

The foundations of the expanded access pathway were laid in the United States (US).[8,9] Prior to the 1980s, access to investigational drugs in the US was an informal process.[10,11] The US Food and Drug Administration (FDA) permitted physicians to prescribe experimental treatments to severely ill patients on a case-by-case basis. The start of the AIDS crisis generated unprecedented attention to the regulatory process and sparked advocacy for broader access to treatments in research and increased patient involvement. Pressure from patient activists led the FDA to

formalize expanded access pathways in 1987, offering regulated access to experimental drugs to thousands of patients facing a life-threatening illness with no other recourse.[12] Similar pathways have since been established around the globe to offer treatment options to patients in need.

Over the years, there has been an increasing interest in expanded access, with various factors potentially causing its rise.[13] External factors, such as improved understanding of the underlying biological mechanism of diseases through research have resulted in an increase in trials investigating potential treatments, in turn leading increased expanded access requests. Likewise, the rise of internet and social media has heightened awareness among patients and physicians of medicine in development.[14] Expanded access itself has also evolved. Over time, familiarity with expanded access has increased, in part due to efforts such as the US 'Project Facilitate' which aims to educate patients, physicians, and industry on expanded access, and intends to improve efficiency in requesting expanded access.[15,16] Companies must publicly post their expanded access policies online,[17,18] and international research databases (e.g., clinicaltrials.gov) offer the ability to register expanded access programs.

Before further examining expanded access and research conducted in tandem with it, we first need a clear and universal definition of expanded access.

Finding common ground: what is expanded access?

There is no globally accepted definition of expanded access. Even more, there is no consensus on the term expanded access itself.[19] In English alone, expanded access is known as 'named-patient use', 'compassionate use', or as 'managed', 'early' or 'special' access, all referring to the provision of unlicensed medicine outside of a trial setting. Non-English speaking countries have implemented local equivalents. For example, the 'authorisation temporaire d'utilisation' or 'accès précoce' in France,[20] the 'Levering op Artsenverklaring' in the Netherlands,[21] the 'Heilversuch' in Austria,[22] and 'el uso compasivo' in Spain,[23] are all analogous to expanded access.

Despite these variations, there are common theoretical principles that define expanded access.[24] Said access pathways are open to patients who are

1. diagnosed with a seriously debilitating or deadly disease;
2. unable to benefit from registered treatment options;
3. disqualified to participate in clinical trials.

The practical process of obtaining access typically involves obtaining informed consent from the patient, a prescription from the treating physician, involvement of a local ethics committee, cooperation from the product manufacturer, and approval from the local regulator.[25,26] These

steps collectively aim to ensure that the potential advantages outweigh the potential side effects. Naturally, the risk/reward balance varies per disease, and changes over time as more evidence becomes available.

Types and timing of expanded access

Expanded access programs are usually split into individual access programs (named-patient use) for single patients, and group programs that simultaneously allow multiple patients to access unregistered medicine.[3] There is no rigid, formal timeline dictating when expanded access can be initiated. In theory, it is possible to request access for any unapproved drug at any stage of development. However, as an investigational product advances through clinical development, evidence accumulates, interest from physicians and patients increases, and single-patient programs can evolve into group access programs.[27] Furthermore, regulators and drug manufacturers are more prone to grant expanded access requests as safety and efficacy become increasingly established.

Additionally, expanded access serves as a means of bridging the time between the completion of regulatory phase III trials and marketing approval. Frequently, drugs are launched in the United States first, making FDA approval the initial endorsement. This approval would spark interest in, for example, Europe, prior to the approval of the European Medicines Agency (EMA).[28] Adding to the confusion, expanded access is not limited to pre-approval access, as it can also be used to access unregistered medicine after they have been withdrawn from the market.

In certain regions, alternate forms of expanded access may be employed if a product has received approval from a regulatory authority outside their jurisdiction, as the associated risks are potentially reduced when another regulator has endorsed the product. Moreover, although not strictly considered 'expanded access', various regulators allow these programs to continue to bridge the time needed to obtain local reimbursement, particularly in countries with a national health system. If a drug is withdrawn from the market for any reason, the product reverts to the 'unapproved' status and, therefore, may strictly qualify for expanded access once more. Figure 1 depicts the relative interest in expanded access over the course of drug development.

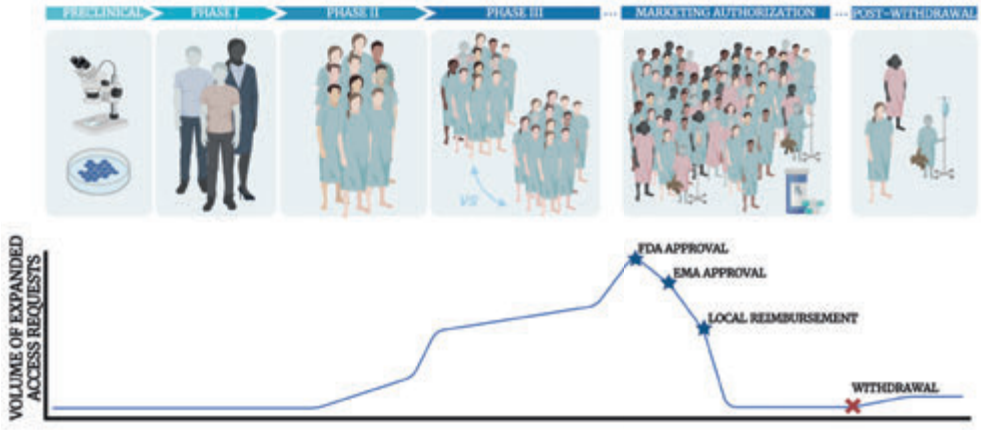

Figure 1: Relative number of expanded access requests over a product's life cycle.

The strict common definition of expanded access would be 'access to a medicine that is unregistered for any indication within its jurisdiction'.

What is typically *not* considered expanded access?

It is important to differentiate between expanded access and other types of unconventional product usage. Off-label usage is not the same as expanded access, as the former occurs when a label is approved in a different indication, and the latter is only possible when the product lacks any regulatory approval. Furthermore, expanded access programs are strictly speaking not synonymous with programs that aim to bridge the time between regulatory approval and reimbursement. Expanded access usually precedes regulatory approval and is not directly linked to reimbursement status. Expanded access is not limited to pre-approval access, as it can also be used post-withdrawal. As these 'peri-approval, peri-reimbursement' situations are simultaneously different and similar, some stakeholders use these terms interchangeably. Understandably, industry frequently employs one 'managed access' desk to handle all request from patients seeking access to drugs that are not available, regardless of whether this is due to a lack of registration or funding.

The multiple stakeholders in expanded access

Patients predominantly hope to benefit from accessing experimental treatments.[29] However, this access is only clinically valuable if the experimental treatments themselves offer advantages. Whether investigational treatments, and thereby expanded access, meet these clinical expectations is unclear. In this thesis, we explore the clinical value of medicine that may be obtained through expanded access.

Apart from patients, expanded access involves a range of stakeholders with varying incentives. Physicians strive to offer optimal treatment options for their patients,[30] companies seek to demonstrate 'compassion', enhance patient/physician engagement, and uphold their reputation,[31] and regulators aim to provide greater access to novel therapies.

Simultaneously, expanded access presents several drawbacks. Patients should not be exposed to unsafe or ineffective treatments, and physicians face an increased workload and may encounter both safety and ethical concerns when prescribing unapproved medicine.[32–34] Companies must bear the cost providing experimental medicine and must dedicate ample resources to navigate differing regulatory pathways, while regulators must balance the needs of current patients without hindering clinical development and thereby endanger broader access to future patients.[4] This thesis examines the practical and ethical dilemmas that can arise from such conflicting interests.

Expanded access programs are primarily designed to provide treatment, and as a result, data of patients that participate in expanded access programs are often overlooked.[35] In fact, some jurisdictions specifically prohibit the collection of data other than safety events in this setting.[22] Nonetheless, there has been growing attention to the potential for expanded access programs to generate evidence. In this way, patients could altruistically contribute to the overall assessment of safety and effectiveness of new medicine, physicians could cooperatively participate in research that informs future clinical decision-making, companies could collect data to support regulatory approvals, reimbursement decisions, or publications, and regulators obtain a broader view of how novel treatments work outside of clinical trial patients. In this thesis, we delve deeper into the value of expanded access as a means to generate evidence.

Generating evidence through expanded access

Generating evidence through expanded access pathways has become a growing area of interest,[36] with anecdotal evidence suggesting that data collected from such programs can be used to inform publications, reimbursement appraisals, and regulatory decision-making.[37] Some countries have even integrated the evaluation of treatments under expanded access pathways in regulatory and

reimbursement decision-making.[38] Despite this growing interest, a systematic overview of the use and integration of expanded access data is absent. As a result, the extent to which these data are used by different stakeholders, such as scholars, patients, or regulators, remains uncertain.

The reliability of data generated through expanded access remains unknown, and evidentiary requirements can vary depending on the intended use.[37,39] For regulatory approval decisions, the highest-grade evidence, such as randomized controlled trials, can be more challenging to be supplemented by expanded access data. For other types of decisions, such as reimbursement decisions, different types of evidence than randomized controlled trials are appropriate. From a quantitative perspective, there is a scarcity of statistical techniques to interpret expanded access data,[40] and these techniques may need evaluation or development to numerically incorporate expanded access.

To what degree the nature of expanded access has changed, who stands to benefit from expanded access research, how, how often, and why data are collected, remains uncertain. Despite the potential benefits, the novel use of expanded access as data generation mechanism raises several concerns, including issues of patient protection, data quality, transparency, financial burden,[41] and research oversight, among others.

Research questions

In this thesis, we will primarily investigate:

- ♣ What are the medical benefits for patients receiving expanded access to experimental treatments?
- ♦ What are the ways in which data obtained from expanded access programs are utilized, and by whom?
- ♥ Can existing statistical techniques be adapted to incorporate data from expanded access programs in the context of analyzing clinical trials?
- ♠ What ethical concerns emerge when using expanded access as a means to generate evidence, and how can improvements be made to expanded access policies?

Methodology

First, we illustrate the practical context of expanded access by providing real-world examples of the strategy, design, monitoring, and analyses of expanded access programs that we were involved in ourselves and inspired the writing of this thesis. In the theoretical context of expanded access, several research topics including ethics, health policy, and statistics warrant further exploration. We address this diverse range of issues by deploying an equally varied research armamentarium.

We developed algorithms to facilitate the analysis of vast amounts of health policy documents, thereby sometimes even having to rely on modern techniques that are able to translate images into text (optical character recognition). In addition, we also made use of standard systematic reviews to answer our research questions. Furthermore, we acquired and analyzed individual patient-level trial data with expanded access data by developing novel statistical techniques, combining Bayesian dynamic borrowing and propensity score matching. Lastly, we investigated the ethical aspects of expanded access research, such as patient selection, access equity, and research oversight, and suggest policy improvements to overcome said concerns. This broad spectrum of research methods was necessary to address the variety of important ethical, practical, statistical, and policy implications that are vital for the future of expanded access.

Outline of this thesis

The structure of this thesis will chronologically follow the progression of our research in four parts. Each part contains several chapters. To guide the reader through our research, we will provide further accompanying prologues and epilogues in between Parts. Hence, the outline described below is deliberately kept succinct.

We start this thesis by providing the reader first-hand insight into two **practical examples** of expanded access programs design, conduct, and publication through two case studies of programs of which we presented the results at several conferences. We will cover all challenges and successes that accompany a real-world expanded access data collection program. As a prelude to the official thesis, we will explain (in Dutch) the way expanded access is regulated in the Netherlands as a reference for Dutch physicians.

♣

In **Part I** will assess the benefits of investigational drugs, as the **clinical merit of expanded access** is contingent upon the drugs it provides access to. The more expanded access is dedicated to highly effective pharmaceuticals, the higher the value of expanded access itself would be. We attempt to quantify the value of experimental drugs by exploring the likelihood that drugs advance through stages of clinical development and relate these probabilities to the assessed clinical benefit of drugs in development and new drugs on the market.

♦

We dedicate **Part II** to **quantify the usage of expanded access data** disseminated through scholarly publications, used by reimbursement bodies, and appraised by regulators. To process this information, we made use of computer algorithms to scan through large bodies of literature. The results of **Part II** form the basis of our further research and provide a basic understanding of when and how data from expanded access are used.

♥

Part III is dedicated to a novel **statistical technique** to incorporate expanded access data into clinical trial analyses. We will explore whether previous scholarship on dynamic borrowing of historical control information, together with more recent statistical advances put forth to include patient characteristics to determine the amount of information to borrow, can be adjusted to help

inform trial data through expanded access programs. We will illustrate our method by analyzing individual patient-level data from the expanded access program and clinical trial of vemurafenib, a treatment for metastatic melanoma. We will evaluate how our method fares compared with traditional methods.

In **Part IV**, we provide means to **improve expanded access policies** to expedite patient access together with evidence generation, discussing several inconsistencies in expanded access policies across jurisdictions. While ethical considerations, including the balance between patient autonomy, informed consent, and the potential for false hope, have been thoroughly discussed by previous scholars,[25,31,42–47] we expand upon their work by addressing the ethical implications of generating evidence through expanded access programs.

Accordingly, we pose an outline of the **ethical considerations** surrounding expanded access research by evaluating if and when the benefits of additional evidence generation outweigh the research strains imposed on patients and physicians, and what policy improvements could be made to harmonize expanded access research in terms of data quality, oversight, and transparency, among others.

Finally, our **postlude** concludes with a **summary** and **discussion**. While the limitations and interpretations of each individual research are described within their respective papers and parts, we dedicate the discussion to address the remainder of overarching issues related to expanded access and this thesis.

PERSONAL MOTIVATION

This thesis was inspired by the practical challenges encountered in my daily work of designing, implementing, and analyzing expanded access programs. I was working for the company myTomorrows, a service provider in the field of expanded access.[1] myTomorrows helps patients and physicians find and access treatment options, and simultaneously designs and conducts expanded access programs for the biopharmaceutical industry. In my daily work, I was responsible for overseeing the data collection and analysis for our clients.

In 2019, I was working on designing a data collection program for pritelivir,[48] an antiviral therapy for treatment-resistant herpes simplex virus, when I started searching for information on how others had implemented expanded access programs. I stumbled upon a single report highlighting examples of the regulatory use of expanded access data for efficacy assessments.[37] This report included lutetium ^{177}Lu dotatate (Lutathera™), a radioactive treatment for pancreatic and gastrointestinal cancers.[49]

The Lutathera program provided access to and collected data from 1,214 patients at a single center,[50] the Erasmus MC in Rotterdam, making my hometown an ideal starting point for future research. Although some informal information was available online, I realized that there was a lack of systematic groundwork to help identify and avoid common pitfalls in executing expanded access programs, as well as an absence of literature on best practices. This sparked my interest and prompted me to embark on the journey of this thesis, aiming to strengthen the theoretical foundation of utilizing expanded access with the hope of addressing my day-to-day issues.

On a personal level, back in 2020, I received a call from an old teammate of my bridge team facing bile duct cancer. By accompanying him to his weekly doctor appointments in Rotterdam, I witnessed firsthand the challenges faced by patients and doctors when no further treatment options are available. Sadly, my friend passed away on March 9th, 2021. I will forever remember our lively discussions on making the most of his remaining days, only a negligible part of these talks was dedicated discussing expanded access and clinical trials, putting the relative importance of the topics discussed in this thesis in perspective.

1 https://mytomorrows.com

CHAPTER I

Data collection in expanded access: real-world examples

Adapted from:

Pritelivir for the treatment of resistant HSV infections in immunocompromised patients: update on an ongoing Phase 3 trial and Early Access Program
Birkmann A, Marini A, Müller A, Polak TB, Rangaraju M, Sumner M, Trübel H, Wald A, Zimmermann H.
STI & HIV, 2023 Chicago (Oral)

Immunocompromised patients with Resistant HSV Infections: Results of the International Early Access Program of Pritelivir
Avery RK, Polak TB, Birkmann A, Truebel H, Gunson S, Sumner M, Dickter J, Neofytos D, and Lee Y.
SSAI/ICHS, 2022 Basel (Poster)

Demographics and Treatment Outcomes in Patients with EBV+ PTLD Treated with Off-the-Shelf EBV-specific CTL (Tabelecleucel) Under an Ongoing Expanded Access Program in Europe: First Analyses
Choquet S, Uttenthal B, Chaganti S, Comoli P, Trappe RU, Friedetzky A, Xing B, Li X, Polak TB, Gamelin L, Terwey J-H, and Dierickx D.
EHA and ASCO, 2022 Vienna, Chicago (Posters)

We here shift our focus from theoretical concepts to practical examples by examining the challenges faced when designing an expanded access program and associated data collection. We will illustrate the design, analyses, and limitations of running an expanded access programs through the lens of two distinct products: pritelivir and tabelecleucel.

1. Pritelivir, an investigational product in infectiology to treat treatment-resistant herpes simplex viruses.
2. Tabelecleucel, a cell therapy for relapsed/refractory patients with a variety of (cancerous) diseases caused in part by Epstein-Bar Virus re-activation in immune compromised patients.

The two programs differ in a variety of aspects, such as the nature of the disease areas, type of product, development stage, and type of company. Pritelivir is a small molecule drug, taken as pill orally by patients at home. Tabelecleucel is an advanced therapy medicinal product, derived from human cells and can only be administered intravenously in specialized hospitals. Second, the marketing authorization submission of tabelecleucel was long underway while the expanded access program started, whereas the phase III trials for pritelivir are still ongoing at the time of writing this thesis.

On a company level, AiCuris is a privately owned smaller biotech company operating from Wuppertal, Germany. In contrast, Atara Biotherapeutics is a NASDAQ (ATRA) listed, publicly traded company, operating from their headquarters in California in the United States. As a result, the reader receives two separate and diverse expanded access examples from both programs.

PRITELIVIR FOR TREATMENT-RESISTANT HERPES SIMPLEX INFECTIONS

Background

Pritelivir is being investigated as a treatment of herpes simplex virus 1 (HSV1) and 2 (HSV2) infections.[51] While nucleoside analogs like acyclovir, (or valacyclovir, famciclovir, and ganciclovir) or phosphonic acid derivatives like foscarnet are the primary treatments for HSV infections, patients may develop resistance to these drugs or experience intolerable side effects, making trials or expanded access programs to drugs in development (like pritelivir) necessary.

Patients with HSV suffer from painful lesions (blisters, sores) that usually appear around the mouth or genital area.[52] Typically, these lesions present in episodes when the immune system is weakened. Immunocompromised patients, such as those living with HIV/AIDS, undergoing stem cell or solid organ transplant, or patients that depend on the use of immunosuppressants, may suffer from HSV infections that last longer, occur more frequently, and are less responsive to conventional therapies. Additionally, patients with persistent HSV infections often present with multiple underlying conditions that weaken their immune system, leading to severe complications from the infections. For example, patients could develop bedsores being unable to sleep due to pain caused by blisters or become morphine-dependent due to the severe pain associated with their HSV infection. For these severely ill patients, physicians sought access to pritelivir when conventional therapies were inadequately effective or safe.

Pritelivir is an anti-HSV helicase-primase inhibitor that is currently in phase III clinical development for the treatment of acyclovir-resistant HSV infections in immunocompromised patients.[53,54] Pritelivir is administered orally through tablets. In the ongoing PRIOH-1 trial (NCT03073967), pritelivir is compared with foscarnet, the only available treatment option for acyclovir-resistant HSV infections. Patients are initially treated with a 28-day course and if clinically necessary, this course may be extended up to 42 days.

Setup and methodology of the expanded access program

In addition to the trial, a global expanded access program was initiated by AiCuris (the sponsor) and myTomorrows (the service provider) for ineligible trial patients in 2019. Apart from the aforementioned medical reasons for ineligibility, there were also several practical reasons patients could not partake in the trial, either sites being fully enrolled, or sites not activated within traveling distance. Additionally, and different from the clinical trial, patients in the expanded access program were allowed to be previously treated with multiple cycles of pritelivir (non-naïve) if lesions re-occurred. Hence, the patient population differed by design from the patients in the trial.

Data were collected through an electronic data collection system (EDC), Castor, that is compliant with all regulatory requirements for a marketing authorization submission. Safety was monitored through standard pharmacovigilance practices. Efficacy was primarily analyzed by in-hospital physician-assessed evaluation of healing of the lesions within 28 or 42 days. Additionally, the assessments could be confirmed by taking both measurements (width times heigh) and photographs of lesions before, during, and after treatment.

The difference in design between the trial and expanded access program led to various choices regarding analysis sets. For example, all patients could be analyzed, including those that were previously treated with pritelivir, hence including patents that had six different courses within the expanded access program multiple times. Else, one could opt to only analyze patients naïve to pritelivir– even excluding patients that had prior successfully been treated in the randomized trial.

Results

With a data cut-off on December 28th, 2022, we analyzed all requests for treatment through expanded access that were received through the online data collection program managed by myTomorrows. The number of requests and subsequently initiated treatment and assessed results are visualized in the flowchart in Figure 2.

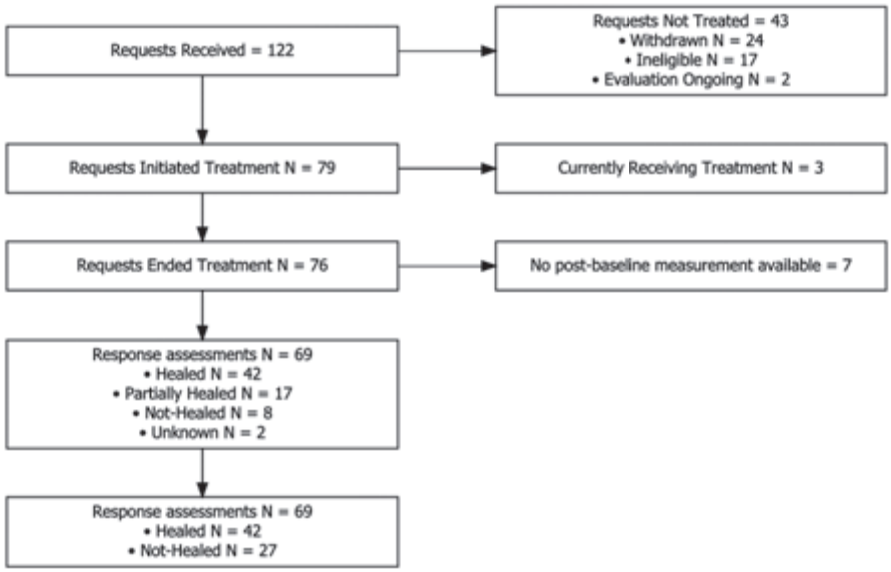

Figure 2: Flowchart of the expanded access program of pritelivir requests and outcomes.

The vast majority of requests 65% (79/122, 95% CI: [56%, 73%]) initiated treatment with pritelivir. These requests concerned 53 unique patients. Requests were received from 11 different countries across Europe, North America, and Africa.

Safety

Zero (0) serious adverse events that were drug-related were reported through the program.

Efficacy

The efficacy of all treatment cycles (including re-treatments) can be seen below (N=69) in Table 1. The high percentage of patients that re-initiated treatments when novel lesions appeared (36%) could be seen as a surrogate indicator of response.

Table 1: Binary efficacy outcomes for pritelivir for all evaluable treatment cycles.

Variable	N = 69[1]	95% CI[2]
Healed after 28-day course (cumulative)	37 (54%)	[41%, 66%]
Healed after 42-day course (cumulative)	42 (61%)	[48%, 72%]

[1]n (%), [2]CI = Confidence Interval

Furthermore, we were also interested in the outcomes of patients that were naïve to pritelivir (i.e., the 'trial' population. Hence, we removed all patients that were re-treated in the EAP (N=23), and we removed patients that were treated in the EAP once but were also treated in the trial (N=4). For all naïve patients (N=69 – 23 – 4 =42), the cumulative outcomes are provided in Table 2.

Table 2: Binary efficacy outcomes for pritelivir for all unique patients that were naïve to pritelivir.

Variable	N	N = 42[1]	95% CI[2]
Healed after 28-day course (cumulative)	42	21 (50%)	[36%, 64%]
Healed after 42-day course (cumulative)	42	25 (60%)	[43%, 74%]

[1]n (%),[2]CI = Confidence Interval

Limitations

1. Due to COVID, patients could not go to the hospital and lesion assessments were made through telephone visit confirmation via the physician, patient self-assessed lesion healing, or sent-through photographs made by patients or family members
2. Although 'perfect' trial patients may have exact squared or circles lesions, we faced a number of patients where the size of lesions was nearly impossible to measure, or certainly not through width times height. We relied on the physician assessment whether or not lesions were healed when exact measurements were unavailable.

3. Due to the sensitivity of the disease, photographic confirmation of the lesion was done on a voluntary basis. We relied on the physician assessment primarily when photographic outcome confirmation was lacking.

Conclusion

At the time of data cut-off, 79 treatment rounds were administered via the expanded access program to 53 patients. The outcomes from the expanded access programs (subgroups) are comparable to the outcomes in the primary randomized controlled trial, where 83% (19/23, 95% CI: [60%, 94%]) healed upon pritelivir initiation. Hence, the expanded access program provides some evidence of the effectiveness of pritelivir in a broad patient population set. Nonetheless, these results have to be interpreted with caution due to the uncontrolled nature of the program, the potential impact of COVID-19 on data quality, and loss of follow-up. The large number of patients requesting re-treatment when lesions re-occurred is an important proxy measure of efficacy that could only be captured in the expanded access program, and not in the ongoing phase III trial.

TABELECLEUCEL FOR EPSTEIN-BARR VIRUS-DRIVEN DISEASES

Background

The second real-life example concerns a living cell therapy called tabelecleucel, developed by Atara Biotherapeutics.[55] Atara Biotherapeutics and myTomorrows initiated an expanded access program to provide tabelecleucel to patients in Europe.[56]

Tabelecleucel (also known as tab-cel®) is an allogeneic, EBV-specific T-cell immunotherapy which targets and eliminates cells infected with the Epstein-Barr Virus. At the initiation of the expanded access program, tabelecleucel was in late clinical development for patients with post-transplant lymphoproliferative disorders (PTLDs). PLTD is a serious and potentially fatal complication in patients that have undergone a transplant, either allogeneic stem cell or solid organ. These patients are severely immunocompromised and thus may not be able to adequately control the virus, which may lead to lymphoproliferation and PTLD. In the program, requests for tabelecleucel could only be accepted if patients were relapsed or refractory to standard treatment options, such as rituximab or chemotherapy regimens, or were ineligible for registered therapies.

Compared with the production of pritelivir in the previous chapter, the production of tabelecleucel is complex. Tabelecleucel is produced from T-cells harvested from human donors. The final products are tested for their capacity of eliminating Epstein-Barr Virus-positive cells in a Human Leucocyte Antigen (HLA)-restricted manner. By producing tabelecleucel with T-cells from different donors, various different cell lines of therapy could be pre-produced and stored in an inventory, making tabelecleucel a cell therapy that is available off-the-shelf. The product is selected for each patient from the existing inventory based on appropriate HLA restriction and allele profile, hence the HLA genotype information from patient and transplant donor is mandatory. Based on response assessment patients could potentially switch to a different cell line with a different HLA restriction as defined in the treatment plan.

Being a cell therapy, there are unique requirements for the storage, handling, transportation, and administration of tabelecleucel. For example, the product is required to be monitored and packaged to ensure stability under extremely low temperatures (≤ -150°C), a process known as cold-chain shipment. As a consequence, only hospital sites with dedicated licenses to meet regulatory standards were allowed to participate in the expanded access program and training for product administration was required to ensure the safe and effective delivery of tabelecleucel to patients.

On the 12th of December 2022, tabelecleucel was registered by the European Medicines Agency under the tradename Ebvallo® for the treatment of relapsed/refractory post-transplant lymphoproliferative disease for patients who test positive for Epstein-Barr Virus.[2]

Setup and methodology of the Expanded Access Program

In addition to the trials, an 'Expanded Access Program' was initiated by the biotech company Atara (the sponsor) and myTomorrows (the service provider) for ineligible trial patients in Europe. The primary goal was to provide treatment to tabelecleucel to patients. Patients were first triaged for participation in clinical trials for tabelecleucel. If participation was impossible, patients were assessed for eligibility for expanded access and determined if treatment could potentially be of benefit to the patient. If appropriately matched product was available and the patient was eligible, the patient could participate in the expanded access program to receive tabelecleucel. In addition to PTLD-patients, patients with different types of diseases driven by the Epstein-Barr Virus could also be considered in the expanded access program, such as primary immunodeficiency-driven lymphoproliferative disease (LPD), acquired immunodeficiency (AID)-driven LPD, smooth muscle tumors (sarcomas including leiomyosarcoma) in line with the clinical development program.

A separate observational study (ATA129-EAP-902) was set-up to describe the patient population, tabelecleucel usage, treatment outcomes, and safety in patients with Epstein-Barr Virus driven diseases treated with tabelecleucel under the expanded access program in Europe (see Figure 3). This observational study required additional consent, as it yearly followed-up on the survival status of patients after the start of tabelecleucel – even when patients were no longer under treatment in the expanded access program.

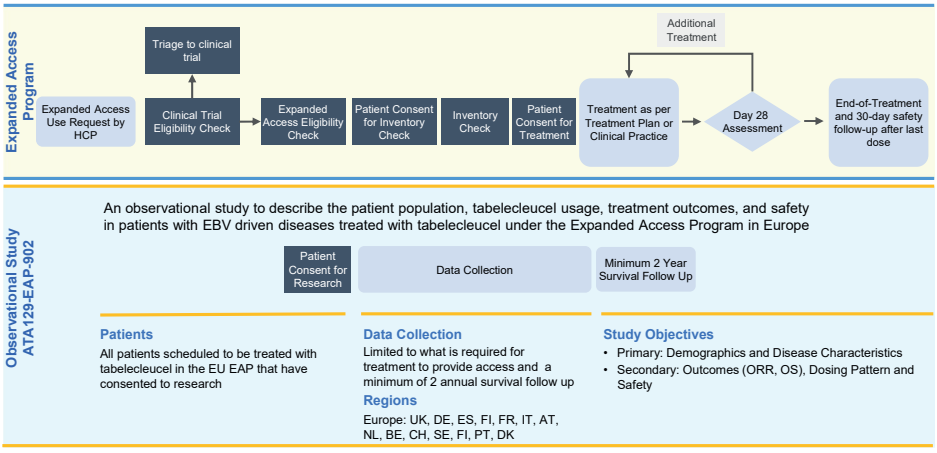

Figure 3: Flowchart for the expanded access program and data collection study for tabelecleucel. Figure adapted from poster publication.[56]

2 https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo

Results

A total of 48 expanded access requests from nine countries for patients with Epstein-Bar Virus driven diseases were received. Twenty-two patients from seven countries consented to this research: 16 Epstein-Bar Virus +PTLD and six Epstein-Bar Virus +non-PTLD. We primarily focused on the PTLD patients. Of the 16 PTLD patients, 15 received at least one dose of tabelecleucel. One patient had not started treatment at data cut-off date.

Safety

No adverse events were reported as related to tabelecleucel by the treating physician. There were no reports of tumor flare reaction, infusion-related reaction, cytokine release syndrome, marrow rejection, or transmission of infectious diseases, including cytomegalovirus. There were no events of graft versus host disease or organ rejection reported as related to tabelecleucel.

Efficacy

The overall response rate as assessed by the treating physicians was 60% (9/15, 95% CI: [32% , 83%]), which is comparable to the overall response rate of 51% (22/43, 95% CI: [35%, 66%]) observed in the pivotal regulatory studies.[55,57]

Limitations

1. Due to the heterogeneity of the disease population, only the results for patients with PTLD are presented. Even within the PTLD-population, variability across disease characteristics, such as viral load or prior therapies, makes it difficult to interpret the results from the expanded access program.
2. Not all patients consented to the research study and are hence lacking from the analysis. Nonetheless, as every cycle response was known, these data are available. How the exclusion of these patients effects the outcomes remains unclear.
3. Assessment of efficacy was done per clinical judgement by each individual treating physician. There was no central blinded review of the outcome results.

Conclusion

The successful implementation and the patient participation of this European program demonstrates the feasibility of administering an off-the-shelf, allogeneic, T-cell therapy and the unmet medical need in this disease area. Although the setting of evidence generation in this program was unblinded, and uncontrolled, the results across benefits and risks reflect the results obtained in the regulatory trials.[57] All adverse events were consistent with the underlying diseases of the patient and were considered unrelated to tabelecleucel. The outcome data for patients with relapsed/refractory PTLD are comparable to data observed in clinical trials. The European expanded access program with Atara Biotherapeutics ended when tabelecleucel received marketing authorization for PTLD patients.[55]

CHAPTER 2

Expanded access in The Netherlands: prescribing unregistered medicine

Expanded Access: het voorschrijven van niet-geregistreerde geneesmiddelen

Polak TB, Cucchi DGJ, van Rosmalen J.

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ENGLISH SUMMARY

Expanded access is a pathway to access unregistered medicines if there are no registered treatments available and patients cannot enroll in clinical trials. For patients who currently are in dire need of treatment options and cannot await drug development processes, or for patient who may benefit from treatments that are not (or not anymore) registered in their jurisdiction, expanded access may serve as a last resort. Unregistered medicine can be acquired via named-patient pathways ('Leveren op Artsenverklaring') or via group programs ('Compassione Use Programma's). We describe the origins of expanded access and its daily practice in the Netherlands. We observe an increasing trend in expanded access requests. Expanded access enables physicians to facilitate access for patients with unmet medical needs. The potential risks these treatments provide, the option to cease further treatment and the preferences of individual patients should all inform the decision whether or not to pursue expanded access.

SAMENVATTING

Expanded access is een toegangsroute tot niet-geregistreerde geneesmiddelen als er geen bewezen effectieve middelen zijn en het onmogelijk is patiënten in onderzoeksverband te behandelen. Voor patiënten die dringend behandeling behoeven en het langdurige ontwikkelproces niet kunnen afwachten, en voor patiënten die gebaat zijn bij een middel dat lokaal niet (meer) is geregistreerd, kan expanded access uitkomst bieden. Niet-geregistreerde geneesmiddelen kunnen worden aangevraagd voor de individuele patiënt (Leveren op Artsenverklaring) of voor patiëntengroepen (Compassionate Use Programma's). Hier beschrijven we hoe expanded access is ontstaan en in de praktijk kan worden uitgevoerd. Wij constateren een toename van expanded access gebruik in Nederland. Met expanded access hebben artsen een belangrijk middel om tegemoet te komen aan onbeantwoorde zorgvragen. De keuze over te gaan tot expanded access dient zorgvuldig te worden afgewogen tegen de risico's van behandeling met experimentele medicijnen, opties tot het staken van verdere behandeling en de wensen van de individuele patiënt.

ACHTERGROND

Artsen mogen geneesmiddelen voorschrijven waarvoor in Nederland een handelsvergunning is afgegeven. Een medicijn krijgt een handelsvergunning, of wordt geregistreerd, als de verwachte positieve effecten opwegen tegen de bijwerkingen. Deze afweging is bij voorkeur gebaseerd op de resultaten van gerandomiseerd, dubbelblind klinisch onderzoek, waarmee de veiligheid van patiënten en de effectiviteit van het middel moeten worden gewaarborgd. De ontwikkeling van een medicijn neemt gemiddeld 12 jaar in beslag, van de ontdekking van het molecuul tot de goedkeuring door toezichthouders.[58] Deze toezichthouders zijn de Food and Drug Administration (FDA) in de Verenigde Staten, het Europees Geneesmiddelen Agentschap (EMA) in Europa en het College ter Beoordeling van Geneesmiddelen (CBG) in Nederland.

Voor sommige patiënten zijn er geen reguliere geneesmiddelen beschikbaar, bijvoorbeeld omdat het middel nog niet in Nederland op de markt is, of omdat het middel is teruggetrokken. Recent onderzoek laat zien dat 2,5% van alle patiënten een onbeantwoorde zorgvraag ('unmet medical need') heeft.[59] Als er een veelbelovend medicijn wordt ontwikkeld, kunnen sommige patiënten niet wachten op goedkeuring, omdat ze bijvoorbeeld een agressieve maligniteit hebben. Ook kunnen deze patiënten vanwege strenge in- en exclusiecriteria vaak niet deelnemen aan trials. Zo komt 7-33% van de patiënten met kanker niet in aanmerking voor deelname aan onderzoek.[60] Toch hebben zij mogelijk baat bij behandeling met een niet-geregistreerd geneesmiddel. Daarom zijn er wettelijke mogelijkheden om aan deze patiënten niet-geregistreerde middelen voor te schrijven.

Hoe is de 'expanded acces'-regeling ontstaan?

In de jaren 80 stonden hiv/aids-activisten en de FDA in een soortgelijk dilemma lijnrecht tegenover elkaar. Er waren geen geregistreerde medicijnen om patiënten met een hiv-infectie te behandelen; veel patiënten konden niet deelnemen aan klinische trials en voor veel patiënten werd aids fataal. Er waren geen richtlijnen voor het gebruik van niet-geregistreerde medicijnen anders dan in onderzoeksverband. Onder druk van patiëntenverenigingen, artsen en de publieke opinie ging de FDA in 1987 overstag en introduceerde de 'expanded access'-regeling.[3,9]

Uitzondering op de Geneesmiddelenwet

Expanded access, ook wel 'early access', 'pre-approval access' of 'compassionate use' genoemd,[19] voorziet in een uitzondering op het verbod op het voorschrijven van niet-geregistreerde geneesmiddelen wanneer aan alle 3 de volgende criteria wordt voldaan: (a) patiënten lijden aan een zeer ernstige of levensbedreigende aandoening (schrijnend geval); (b) geregistreerde adequate alternatieve geneesmiddelen zijn niet aanwezig; en (c) patiënten kunnen niet deelnemen aan klinisch onderzoek.[24]

Normaal gesproken verbiedt de Geneesmiddelenwet geneesmiddelen beschikbaar te stellen waarvoor in Nederland geen handelsvergunning is afgegeven. Er bestaan uitzonderingen voor bijvoorbeeld studiemedicatie of geneesmiddelen die door een apotheker zelf worden bereid. Expanded access is een aanvullende uitzondering, waarvoor veel aandacht was rondom het gebruik van niet-geregistreerde medicatie voor de behandeling van patiënten met covid-19. Expanded access is iets anders dan offlabelgebruik. Offlabelgebruik wil zeggen dat geregistreerde geneesmiddelen buiten de geregistreerde indicatie worden gebruikt. Een voorbeeld hiervan is dat hydroxychloroquine en chloroquine werd gebruikt voor de behandeling van patiënten met ernstige covid-19. In Nederland valt offlabelgebruik níet onder expanded-accesswetgeving. Alleen geneesmiddelen die op het moment van voorschrijven in Nederland geen enkele registratie hebben vallen onder deze wetgeving.

Er zijn twee manieren om een niet-geregistreerd geneesmiddel voor te schrijven via expanded access: (a) via het zogenoemde leveren op artsenverklaring en (b) via 'compassionate use'-programma's (CUP's).

LEVEREN OP ARTSENVERKLARING

Leveren op artsenverklaring wordt gebruikt voor individuele aanvragen om een niet-geregistreerd geneesmiddel voor te schrijven.[61] Dit staat ook bekend als 'named-patient use'. Daarbij moet de behandelend arts een verklaring opstellen, waarin die verklaart dat: (a) de patiënt niet adequaat behandeld kan worden met geregistreerde medicatie en daarom een niet-geregistreerd geneesmiddel nodig heeft; (b) de patiënt nadrukkelijk is geïnformeerd over het niet-geregistreerde middel en de daarbij behorende risico's; (c) de arts de volle verantwoordelijkheid draagt en de risico's voor behandeling aanvaardt; en (d) de arts alle aan het middel gerelateerde bijwerkingen meldt.

Behalve de bovengenoemde voorwaarden zijn er géén beperkingen voor het gebruik van niet-geregistreerde geneesmiddelen. Het middel hoeft niet elders goedgekeurd te zijn en hoeft niet een bepaalde fase van ontwikkeling doorlopen te hebben; leveren op artsenverklaring is mogelijk bij geneesmiddelen in fase I, fase II of fase III van de ontwikkeling. Wel geldt: hoe verder in het ontwikkeltraject, hoe meer inzicht er is in de verhouding tussen de risico's en de baten.

Het is ook mogelijk om middelen die in Nederland niet meer geregistreerd zijn, zoals levosimendan,[62] voor te schrijven via het leveren op artsenverklaring. Termen als 'early access' en 'pre-approval access' doen echter anders vermoeden, waardoor we wellicht beter kunnen spreken van 'post-withdrawal' of 'late access'.

Met een artsenverklaring kan een apotheker, groothandelaar, fabrikant of apotheekhoudende huisarts een verzoek indienen bij de Inspectie Gezondheidszorg en Jeugd (IGJ). De inspectie beslist over het verzoek en specificeert een geldigheidsduur wanneer zij de aanvraag goedkeurt (normaal gesproken 1 (één) jaar). De fabrikant van het betreffende geneesmiddel bepaalt zelf of hij op dit verzoek ingaat. Dus goedkeuring van de IGJ voor het leveren op artsenverklaring garandeert niet dat het geneesmiddel ook daadwerkelijk beschikbaar wordt gesteld. In de meeste gevallen wordt het middel gratis ter beschikking gesteld; incidenteel vraagt de fabrikant een vergoeding.[24]

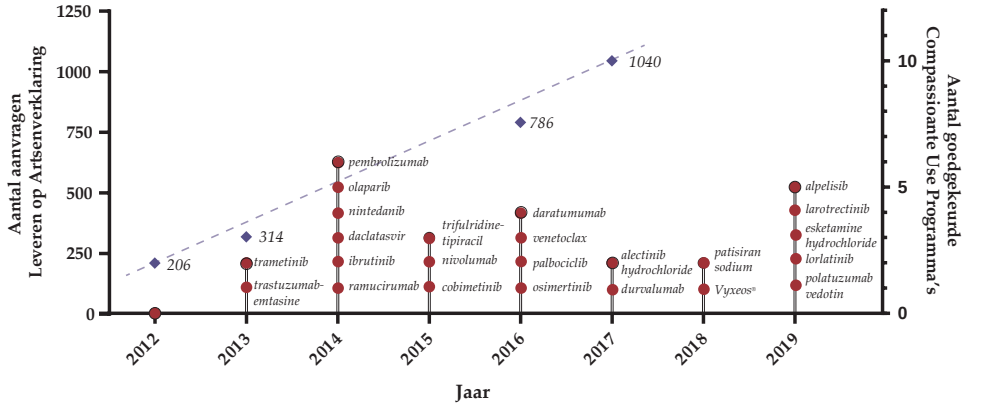
COMPASSIONATE-USEPROGRAMMA'S

Een CUP kan worden ingezet om meerdere patiënten met niet-geregistreerd geneesmiddel te behandelen.[63] De patiënten die voor deze behandeling in aanmerking komen worden duidelijk omschreven. Om een CUP op te kunnen starten moet de fabrikant van het geneesmiddel zelf een verzoek indienen bij het CBG. Naast de drie algemene voorwaarden om in aanmerking te komen voor compassionate use, moet er uitzicht zijn op spoedige registratie, bijvoorbeeld via een lopende registratieprocedure. Daarom kan pas laat in het ontwikkeltraject van een geneesmiddel een CUP worden opgezet. Omdat het CBG betrokken is bij de registratiefase van het geneesmiddel, is zij de toezichthouder op het CUP, anders dan bij het leveren op artsenverklaring, waar de IGJ op toeziet.

De CUP's die zijn goedgekeurd staan op de website van het CBG en zijn samengevat in de figuur.[64] In 2020 gold dit voor risdiplam bij patiënten met spinale musculaire atrofie en – totdat het op de markt kwam – voor remdesivir bij patiënten met covid-19. Een apotheker of arts kan het geneesmiddel uit het CUP direct aanvragen bij de fabrikant van het middel. Een positief besluit van het CBG is gedurende een jaar geldig en kan nadien worden verlengd.

EXPANDED ACCESS IN NEDERLAND

Het aantal aanvragen per jaar voor het leveren op artsenverklaring is gestegen, van 206 in 2012 tot 1,040 in 2017 (Figuur 4).[65–67] Dit is een gemiddelde stijging van 38% per jaar. Recentere cijfers zijn nog niet beschikbaar. Het is goed mogelijk dat de cijfers voor 2020 verder omhooggestuwd worden, onder meer door de vraag naar experimentele behandelingen voor patiënten met covid-19.



Figuur 4: Overzicht van het aantal aanvragen voor Leveren op Artsenverklaring (LoA, magenta ruiten, linker y-as) en Compassionate Use Programma's (CUPs, donkerrode bollen, rechter y-as) tussen 2012 en 2019. Het aantal aanvragen voor LoA in is afgeleid uit antwoorden op Kamervragen en jaarverslagen IGJ 2016 en 2017.[65–67] Voor de jaren 2014 en 2015 zijn voor LoA geen openbare data beschikbaar. De stippellijn geeft de gemiddelde toename tussen 2012 en 2017 weer. Data voor goedgekeurde CUPs zijn afkomstig van de website van het College ter Beoordeling van Geneesmiddelen.[68] Het CBG registreert niet hoeveel individuele patiënten gebruik maken van een CUP. Gegeven zijn de generieke namen van geneesmiddelen waarvoor een CUP werd goedgekeurd in het aangegeven jaar. Vyxeos is de merknaam voor de liposomale bereiding van cytarabine en daunorubicine.[64]

Wie komt in aanmerking?

Idealiter behandelen artsen hun patiënten volgens de geldende richtlijnen met een geregistreerd geneesmiddel. Wanneer er geen geregistreerde middelen voorhanden zijn, geniet het de voorkeur dat patiënten deelnemen aan klinische studies naar de werkzaamheid en veiligheid van een niet-geregistreerd geneesmiddel. Soms is het deelnemen aan onderzoek echter geen optie. Redenen daarvoor kunnen zijn dat er geen patiënten meer worden geïncludeerd of dat de patiënt niet voldoet aan de inclusiecriteria van het onderzoek naar het niet-geregistreerde geneesmiddel. Soms wordt het onderzoek niet in Nederland verricht of loopt er op dat moment helemaal geen onderzoek naar het niet-geregistreerde geneesmiddel. Wanneer deelname aan klinisch onderzoek niet mogelijk is kunnen patiënten in aanmerking komen voor expanded access. Expanded access kan ook worden gebruikt als het geneesmiddel wel in een ander land is geregistreerd, maar nog niet of niet meer in Nederland.

Gegevens voor registratie van het geneesmiddel

Expanded access wordt veel gebruikt voor patiënten met een (hemato-)oncologische ziekte of een weesziekte. Weesziekten zijn aandoeningen die voorkomen bij minder dan vijf op de 10,000 mensen. In het verleden zijn er in Nederland grote CUP's geweest om bijvoorbeeld imatinib voor patiënten met chronische myeloïde leukemie en lenalidomide voor patiënten met multipel

myeloom beschikbaar te maken. Hier zijn wetenschappelijke publicaties over verschenen en de registratieaanvragen van beide geneesmiddelen zijn aangevuld met de gegevens uit deze programma's.[69,70] In het NTvG is eerder beschreven hoe de registratie van lutetium-octreotraat voor de behandeling van patiënten met neuro-endocriene tumoren deels gestoeld is op de gegevens van patiënten uit het Erasmus MC die met het middel werden behandeld via een CUP.[50] Fabrikanten van geneesmiddelen vullen gegevens uit conventioneel klinisch onderzoek steeds vaker aan met gegevens uit expanded-accessprogramma's wanneer zij een aanvraag doen voor registratie van een geneesmiddel.[71] Hoewel de resultaten van gerandomiseerde, dubbelblinde trials het betrouwbaarst zijn, geven de gegevens uit expanded-accessprogramma's inzicht in de werkzaamheid en veiligheid bij patiënten die niet in de onderzoekspopulatie vallen.

Afwegingen

Het is cruciaal dat de arts en de patiënt samen een goede afweging maken tussen de potentiële toegevoegde waarde van een behandeling met een niet-geregistreerd geneesmiddel en de tijd en inspanning die het van hen vergt. Het ligt voor de hand om via expanded access voornamelijk geneesmiddelen voor te schrijven die al ver ontwikkeld zijn en waarvan een groot therapeutisch effect wordt verwacht. Het merendeel van de geneesmiddelen dat wordt ontwikkeld blijkt later niet effectief te zijn en wel schadelijke bijwerkingen te hebben. Een van de pioniers van de RCT en de systematische review, Thomas C. Chalmers (1917-1995), verwoordde het als volgt: 'One only has to review the graveyard of discarded therapies to discover how many patients have benefited from being randomly assigned to a control group.'[72] Bij de keuze voor een behandeling met een niet-geregistreerd geneesmiddel moeten de arts en de patiënt ook overwegen om af te zien van verdere behandeling. Een kleine Nederlandse studie liet zien dat patiënten die niet meer in aanmerking kwamen voor medicamenteuze behandeling graag op de hoogte worden gesteld van alle mogelijke vervolgstappen, zoals expanded access.[29]

In andere landen gaat een expanded-accessaanvraag langs een medisch-ethische toetsingscommissie vanwege de complexe afweging die erbij komt kijken.[3] In Nederland ligt de verantwoordelijkheid voor een zorgvuldige overweging bij de behandelend arts.

Waarom gebruiken we expanded access vaker?

In Nederland wordt er steeds vaker gebruikgemaakt van expanded access. Patiënten zijn steeds vaker op de hoogte van niet-reguliere behandelopties, bijvoorbeeld via online-initiatieven, zoals www.reaganudall.org, www.patientslikeme.com en www.mytomorrows.nl.[14,24] Daarnaast zijn expanded access-programma's tegenwoordig ook geregistreerd op www.clinicaltrials.gov en zijn Amerikaanse fabrikanten verplicht om een beleid te hebben voor het beschikbaar stellen van niet-geregistreerde geneesmiddelen via expanded access. Zolang slechts een selecte groep

patiënten kan deelnemen aan klinisch onderzoek, zullen er patiënten blijven die in aanmerking willen komen voor behandeling met een niet-geregistreerd geneesmiddel.

De FDA en de EMA verschillen in de snelheid waarmee zij een registratieaanvraag voor een nieuw geneesmiddel beoordelen. Dit verschil kan een reden zijn waarom expanded access in Nederland steeds vaker wordt gebruikt. Er is meer onderzoek nodig om te identificeren wat het stijgende aantal expanded access-aanvragen in Nederland nog meer veroorzaakt.

Conclusie

Expanded access biedt een mogelijkheid om patiënten met niet-geregistreerde geneesmiddelen te behandelen wanneer behandeling met een geregistreerd geneesmiddel niet mogelijk is en zij niet in onderzoeksverband behandeld kunnen worden. In Nederland wordt steeds vaker gebruikgemaakt van expanded access en dit reflecteert de toegenomen vrijheid die patiënten hebben bij de keuze voor een behandeling. Bij de keuze voor een behandeling met een niet-geregistreerd geneesmiddel moeten de verwachtingen van de patiënt realistisch zijn, aangezien de werkzaamheid en veiligheid van het middel niet altijd overtuigend zijn aangetoond. Het afzien van verdere behandeling blijft een belangrijk alternatief. De arts en de patiënt kunnen dan weloverwogen kiezen voor behandeling met een niet-geregistreerd geneesmiddel. Idealiter vindt die behandeling plaats in onderzoeksverband en anders via expanded access.

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PART I

The clinical merit of expanded access

PROLOGUE

A critical challenge is determining the extent to which expanded access objectively improves patient outcomes. As expanded access provides patients access to drugs in development, one needs to evaluate the clinical benefit of drugs under development to derive an estimate of the merits of expanded access itself.

Understanding the added clinical benefit of expanded access requires an assessment of the clinical benefits of drugs in development and their likelihood of reaching the market. Assessing benefit of investigational drugs is inherently complicated, as, by definition, these drugs are under investigation. Moreover, determining the benefit of access to early-phase investigational drugs is more complicated than determining benefit to drugs in later stages of development. For example, the interpretation of phase II trials is frequently hampered by a lack of randomization, limited patient numbers, different dosing schedules, among others. Expanded access to phase II drugs may be less likely to provide benefit, as many phase II trials do not progress to phase III.

Evaluating the clinical merit of drugs under development itself it highly complicated, and evaluating expanded access to said drugs is even more complex. Nonetheless, we will here attempt to derive a proxy measure to evaluate the benefits patients may derive by accessing investigational drugs through expanded access.

First, we will look at the probabilities of drugs advancing through phases of clinical development. Throughout the development process, drugs may be discontinued due to an unfavorable benefit/risk profile. As a result, access to drugs in later stages of development increases the chances of accessing drugs that are more likely to provide benefit.

Second, we can estimate the clinical benefit of new drugs based on data derived from clinical trials or cost-effectiveness analyses. We do so by looking at drugs still recently developed for hematologic malignancies, and looking at drugs that have obtained institutionalized reimbursement in the United Kingdom, meaning they are readily available on the market. We take two approaches in assessing clinical benefit of drugs. The first approach involves specialized disease scales, which are designed to estimate a pre-defined level of clinical benefit within a specific disease area, in this case hematology. The other approach employs a universal metric called the quality-adjusted life year (QALY), enabling comparisons of drug benefits across different disease areas.

By comparing the benefits of drugs in development, considering the probabilities of drugs advancing to marketing approval, and factoring in the number of access programs or patients within these programs, in this part we will derive a proxy measure of the clinical value of drugs provided through expanded access.

CHAPTER 3

The clinical value of drugs under development in hematological malignancies

Adapted from:

Two decades of targeted therapies in acute myeloid leukemia
Polak TB, Cucchi DGJ, Ossenkoppele GJ, Uyl-De Groot CA, Cloos J, Zweegman S, Janssen JJWM.
Leukemia. 2021 Mar;35(3):651-660.

The predictive value of a positive phase II ASH abstract for peer-reviewed publication and progression to phase III
Cucchi DGJ, Polak TB, Ossenkoppele GJ, Rowe JM, Estey EH.
Blood. 2022 Mar 24;139(12):1920-1923.

WEIGHING POSITIVE PHASE II RESULTS FOR EXPANDED ACCESS

Novel agents are often lauded as 'life-changing' or 'breakthrough' when showcased at scientific conferences.[1,2] These events often serve as the initial introduction of new drugs to physicians, and the positive portrayal in posters or abstracts may later lead to potential requests for expanded access. We wondered whether abstracts presenting 'positive' outcomes at the major global hematology conference, the meetings of the American Society of Hematology (ASH) of phase II drugs eventually were associated with the initiation of a phase III investigations and potentially subsequent drug approvals.

For this research, we tabulated all abstracts on hematological malignancies of three consecutive years of ASH meetings, 2013-2015. Abstracts were categorized as 'positive', 'negative', or 'inconclusive' (Table 1). Positive abstracts featured terms such as 'encouraging', 'promising', 'could represent a novel therapeutic option' and 'warrants investigation in a randomized trial'. 'Negative' abstracts included terms such as 'does not support further research' and 'demonstrates no clinical activity'. The remainder were scored as inconclusive. We also assessed the reliability of 'positive' abstracts by determining if the results were published in peer-reviewed journals with the 'positive' outlook maintained, and if a phase III trial was initiated with the described drug.

We found that the large majority of presented abstracts were 'positive' (76%), and that results from both 'positive' and 'negative' abstracts were published at a similar rate in peer reviewed journals (83% and 86% respectively). And although results are initially presented as promising, only 47% of regimens described in 'positive' abstracts progressed to phase III.

Table 1: Research characteristics according to abstract conclusion as presented at ASH 2013 to 2015

	OVERALL	INCONCLUSIVE	NEGATIVE	POSITIVE
YEAR				
2013	124	20 (16%)*	11 (9%)	93 (75%)
2014	128	16 (13%)	13 (10%)	99 (77%)
2015	116	3 (3%)	13 (11%)	100 (86%)
SAMPLE SIZE	41 (25-63)†	41 (26-69)	29 (21-53)	41 (25-63)
PUBLISHED	302 (82%)‡	28 (72%)	32 (86%)	242 (83%)
PHASE III	161 (44%)	13 (33%)	11 (30%)	137 (47%)
TOTAL	368	39	37	292

*N (percent per year). †Median (interquartile range). ‡N (percent per abstract conclusion).

Although provision of drugs in phase II through expanded access is less common than drugs that are under investigation in phase III,[3] the positive presentation of early-phase drugs may prompt physicians to consider requesting expanded access to phase II drugs as well. Based on our findings, we recommend physicians to exercise caution when requesting expanded access on the basis of positive poster presentations in phase II.

The initial enthusiasm surrounding these therapies may be overstated, as they do not always result in consistent positive outcomes in peer-reviewed research,[4] and frequently are not associated with initiation of a phase III trials. Although there may be other reasons than lack of clinical benefit to dismiss a phase III trial, the absence of progression can be viewed as an indirect measure of the new drug's potential and, consequently, its suitability for expanded access. On the other hand, we will see in the next chapter that drugs that initially fail a first phase II trial are not by definition 'ineffective'. They may subsequently successfully complete a different phase II trial aimed at a different line of therapy or a different patient population.

THE CLINICAL BENEFITS OF DRUGS DEVELOPED FOR ACUTE MYELOID LEUKEMIA

Next, we focused on a single disease in hematology, to better be able to compare novel drugs under development. In line with evaluating the predictive value of 'positive' conclusions for progression of a drug through phase II to phase III, we here evaluated if and how novel agents progressed from phase II to phase III to FDA approval, and in addition evaluated the clinical benefit these drugs using specialized disease benefit scales.

We focused on the hematological malignancy of acute myeloid leukemia (AML). Research – and expanded access - in hematology is primarily devoted to studying treatments for hematological malignancies, rather than benign conditions (e.g., anemia, sickle cell disease), and AML is a hematological malignancy with a high disease burden: the 5-year overall survival rate is 28%.[5] This percentage is even lower for elderly patients, who are unable to qualify for stem cell therapy, the only curative treatment. Until 2016, the only approved treatment options for AML were chemotherapy and stem cell transplantation, which consistently induce serious and sometimes life-threatening toxicities.[6] Moreover, despite intensive therapy, most patients eventually relapse, and subsequently have very dismal survival rates.[7]

Since the remarkable discovery of imatinib for chronic myeloid leukemia,[8] hopes for more successful targeted therapies to treat other hematological malignancies have skyrocketed. Although AML is not characterized by a single genetic aberration such as chronic myeloid leukemia, myeloid cells express various targetable proteins which has led to a surge in development of targeted

therapies in AML. Therefore, we evaluated targeted drug development during twenty years of clinical research in AML based on progression of distinct drugs from phase II to phase III to FDA-approval. Additionally, we assessed the benefits through the Magnitude of Clinical Benefit Scale (MCBS) of the European Society for Medical Oncology (ESMO).[9] Through a combination of study type (randomized or not), setting (curative or non-curative), endpoints (quality of life, survival, response rates), and statistical significance, the ESMO-MCBS v1.1 is developed specifically to evaluate the clinical benefit of oncology drugs, and has been successfully adopted in the assessment of hematological drugs. A detailed explanation of this scale can be found in the work of Kiesewetter and colleagues.[10]

We searched for trials in AML in ClinicalTrials.gov, and categorized all studies based on drug, target, and clinical end points. We found that between January 2000 and September 2020, 167 distinct pharmaceutical agents with 96 targets were investigated in 397 phase II trials (Figure 1).

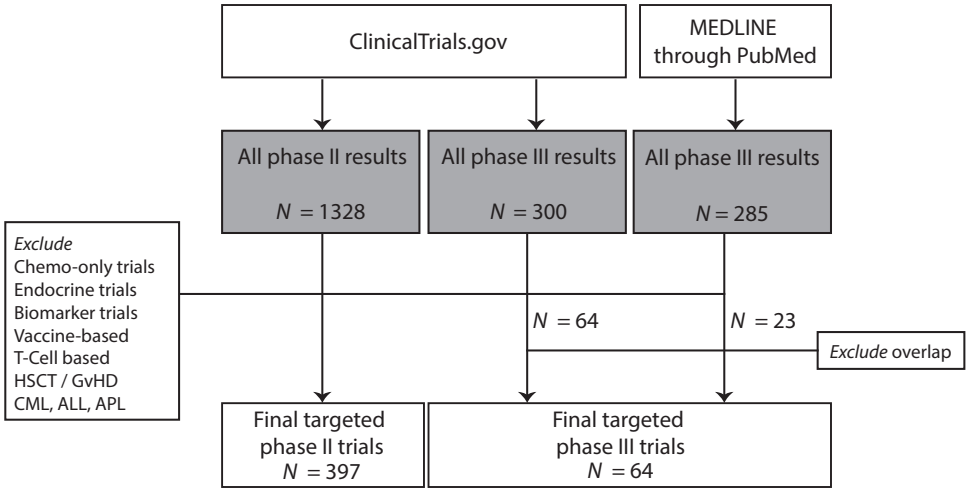


Figure 1: Search strategy. Phase II and III trials were identified through ClinicalTrials.gov. Additional published phase III trials were identified in MEDLINE through PubMed. Of the phase III trials, we evaluated whether published results were available that were not yet identified in the PubMed search.

Results

Twenty-eight agents were steered towards phase III, after three phase II trials on average, across a variety of different potential targets (Figure 2). In this Figure, one also sees the multiplicity of phase II trials prior to progressing to phase III research. This underlines the uncertainty inherent to early-stage clinical development, in which the exact dosage, setting, and patient populations that might benefit from investigational drugs still has to be determined.

Eight targeted drugs were FDA approved. Of these, none had been proven to improve quality of life at time of approval. Systematic evaluation through the ESMO-MCBS v1.1 indicated that two out of eight drugs provide substantial benefit, but three out of eight approved products had not established a clinically relevant gain in overall survival at the time of approval (see Table 2). Ongoing development of targeted agents and application in combination with chemotherapy raise new perspective for patients with AML, and provide them with some survival benefit. However, objectively, only 16.8% of 167 targeted agents (potentially provided to patients through expanded access) moved to phase III and of the eight FDA approved drugs, a minority provides a substantial clinical benefit.

Thus, returns on targeted therapy research remain lean for AML patients, and so potentially does expanded access to these drugs. Accessing drugs in early stages of development, whether it is through trial participation or through expanded access pathways, usually simply equates to accessing ineffective therapies.

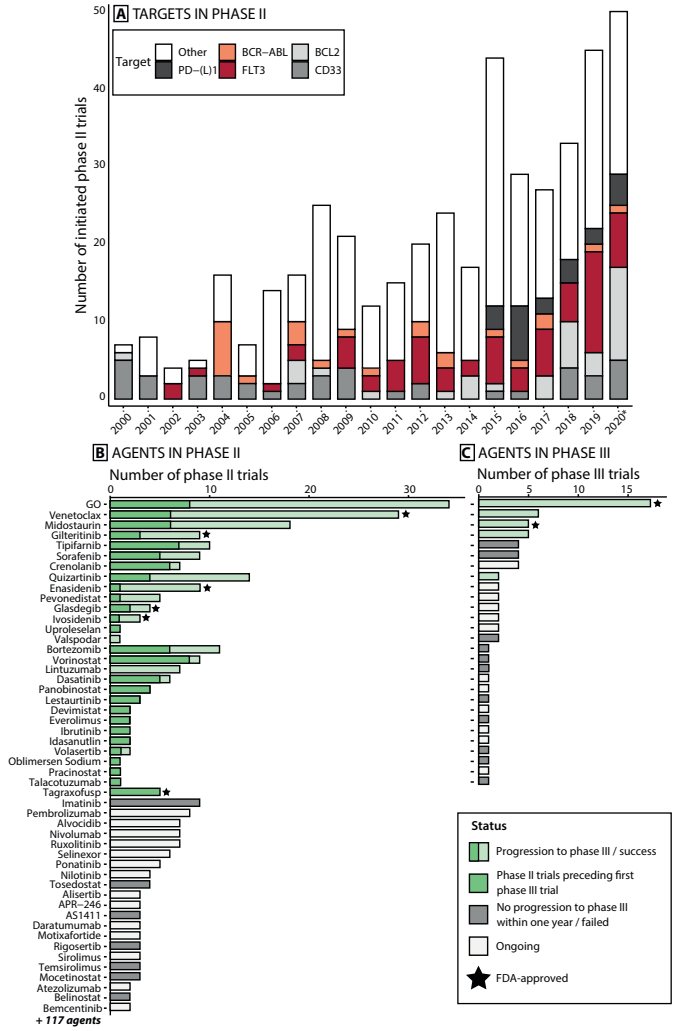


Figure 2: Targets and targeted agents in phase II and II clinical trials.

A Overview of trials initiated each year from 2000 to September 2020. Top five targets, based on number of trials, are annotated in the bar plots.

B Overview of top-50 targeted agents investigated in phase II clinical trials. In total, we observed 167 individual agents in phase II research for the treatment of AML between 2000 and September 2020.

C Overview of targeted agents investigated in phase III clinical trials. Bars are annotated based on progression to phase III, phase III result and FDA approval. Furthermore, bars in phase II are annotated with the number of phase II trials initiated before the first phase III trial of that agent started. Position of FDA-approval indication depends on the pivotal trial on which approval was based. The primary target of each investigated agents is displayed. This implicates that the agents investigated in these trials may have been selected because of the expected benefit of modulation of targets other than the primary target of that agent (e.g., C-KIT inhibition by imatinib, of which the primary target is BCR-ABL).

* Results are shown for January 2020 through September 2020.

Table 2: Magnitude of clinical benefit of FDA-approved targeted agents for the treatment of acute myeloid leukemia (AML).

Treatment regimen & FDA approval date	OS/EFS Control Group	OS/EFS gain or ORR	Other outcome measures (exp vs control or exp arm)	Toxicity	ESMO-MCBS v1.1 Score	Magnitude of Clinical Benefit
SOC +/- Gemtuzumab Ozogamicin September 2017	EFS: 17.1% 2 y	EFS 23.7%, HR 0.58 (0.43 - 0.78)	CR+CRp: 81% vs 75% OS: 34.0 mo vs 19.2 mo	Increased	A	Major
LD Decitabine +/- GlasdegiB November 2018	OS: 4.9 mo	OS: 3.9 mo 0.51; 80% CI, 0.39–0.67	CR: 17.0% vs 2.3% ORR: 26.9% vs 5.3% Duration of CR: 6.5 mo Duration of ORR: 9.9 mo.	Slightly increased	4	Substantial
SOC +/- Midostaurin April 2017	OS: 25.6 mo	OS: 49.1 mo, HR 0.78 (0.63 - 0.96)	CR: 58.9% vs 53.5% EFS: 8.2 mo vs 3.0 mo	Similar	A	Major
Tagraxofusp December 2018	N/A	CR + CCR: 72%	ORR: 90%	N/A	3	Moderate
Venetoclax + decitabine or azacitidine October 2020	N/A	68% ORR	CR+CRi: 67% Duration of CR+CRi: 11.3 mo Median OS: 17.5 mo	N/A	2	N/A
AZACITIDINE +/- VENETOCLAX October 2020	OS: 9.6 mo	OS: 5.1 mo	CR+CRi: 66.4% vs 28.3% Duration of CR+CRi: 17.5 mo vs 13.5 mo.	Increased	4	Substantial
Enasidenib August 2017	N/A	ORR 40.3%	CR: 20.2% vs 19.3%	N/A	2	N/A
Gilteritinib or Salvage Therapy November 2018	OS: 5.6 mo	OS: 3.7 mo, HR 0.64 (0.49-0.83)	CR+CRp: 34.0% vs 15.3% ORR: 67.5% vs 25.8%	Slightly decreased	4	Substantial
Ivosidenib July 2018	N/A	22% CR, ORR 42%	Duration of CR: 8.2 mo Duration of ORR: 6.5 mo.	N/A	2	N/A

Overview of pivotal trials for the FDA-approval of targeted agents for the treatment of AML. ESMO-MCBS scores for midostaurin, gemtuzumab ozogamicin and enasidenib were adopted from Kiesewetter et al.[10]. The highest grades of the ESMO-MCBS in the curative setting are A and B. A indicates a major, and B indicates an important benefit. In the non-curative setting, scores 4 and 5 indicate a substantial benefit. 3 indicates a moderate benefit. The endpoint used for EMSO-MCBS classification is printed italic.

EXP experimental, SHh sonic hedgehog, OS overall survival, EFS event free survival, CR complete remission, CRp complete remission with incomplete platelet recovery, CRi complete remission with incomplete hematologic recovery, ORR overall response rate, R/R relapsed/refractory, LD low-dose, SOC standard of care, REF reference, HR hazard ratio, mos. months, y/o years old, N/A not applicable/no measure of magnitude of clinical benefit based on ESMO-MCBS v.1.1 CI confidence interval, ESMO-MCBS v1.1 European Society for Medical Oncology—Magnitude of Clinical Benefit Scale version 1.1.

CHAPTER 4

Incremental benefits of novel pharmaceuticals in the United Kingdom: A cross-sectional analysis of NICE technology appraisals from 2010 - 2020

Polak TB, Cucchi DGJ, Darrow JJ, Versteegh MM.
BMJ Open. 2022 Apr 8;12(4):e058279.

ABSTRACT

Objectives: To evaluate the incremental value of new drugs across disease areas receiving favorable coverage decisions by the United Kingdom's National Institute for Health and Care Excellence (NICE) over the past decade.

Design, setting, and participants: This cross-sectional study assessed favorable appraisal decisions of drugs between January 1st, 2010 and December 31st, 2020. Estimates of incremental benefit were extracted from NICE's evidence review groups reports.

Primary outcome measure: Incremental benefit of novel drugs relative to the best alternative therapeutic option, expressed in Quality Adjusted Life Years (QALYs).

Results: 184 appraisals of 129 drugs provided QALYs. The median incremental value was 0.27 QALY (interquartile range[IQR]: 0.07-0.73). Benefits varied across drug-indication pairs (range: -0.49-5.22 QALYs). The highest median benefits were found in hematology (0.70 QALY, IQR: 0.55-1.22) and oncology (0.46 QALY, IQR: 0.20-0.88), the lowest in ophthalmology (0.09, IQR: 0.04-0.22) and endocrinology (0.02, IQR: 0.01-0.06). Eight appraisals (4.3%) found contributions of more than two QALYs, but one in four (50/184) drug-indication pairs provided less than the equivalent of one month in perfect health compared to existing treatments.

Conclusions: In our review period, the median incremental value of novel drugs approved for use within the English NHS, relative to the best alternative therapeutic option, was equivalent to three to four months of life in perfect health, but data were heterogeneous. Objective evaluations of therapeutic value help patients and physicians to develop reasonable expectations of drugs and delivers insights into disease areas where medicinal therapeutic progress has had the most and least impact.

INTRODUCTION

Before a novel treatment is allowed on the market, its clinical benefit is assessed by regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). However, clinical benefit evaluations do not provide insight into issues deemed relevant by payers, such as comparative effectiveness, cost effectiveness, or lifetime benefit. Therefore, several countries have created independent health technology assessment bodies to conduct drug value assessments, commonly referred to as cost effectiveness analyses.[11] Through these value assessments, publicly-funded experts help to clarify the incremental clinical benefit and incremental costs of selected new therapies according to their approved indications, which professional societies may then rely on when revising treatment guidelines to include the new drug.

Despite the increased focus on incremental drug value, surprisingly little attention has been devoted to understanding the magnitude and distribution of their clinical benefits across disease areas. The limited scholarship in this area can be explained in part by the fact that, until recently, it has been difficult to compare the benefit of drugs intended to treat widely divergent diseases or conditions.

However, the emergence of official government drug value assessments over the past two decades, rigorously conducted following a consistent set of health economic modelling guidelines, now makes such comparisons feasible. These assessments utilize the Quality Adjusted Life Year (QALY), a common metric of patient health. One QALY, for example, represents the equivalent of one additional year of life in perfect health, or some longer period of time in less-than-perfect health.[12,13] Although the QALY has long been available as a measure and is frequently used in individual economic evaluations,[14] the QALY can, in combination with forecasts over the lifetime of patients from health economic models, be used to compare health benefits across medical disciplines in a consistent and transparent manner. QALYs are primarily used to calculate incremental cost-effectiveness ratios (ICER), which signals the efficiency with which a health technology produces health by dividing incremental costs by incremental benefits expressed as QALYs. However, it is often overlooked that the QALY part of an ICER is, in and of itself, a parameter that provides relevant insights into the size of forecasted health benefit. In the case of the UK, QALYs are produced following specific modelling guidance by the National Institute for Health and Care Excellence (NICE), enhancing their comparability across diseases.

NICE is a non-departmental public body that assesses the value of novel drugs and the impact on the English National Health System (NHS) of adopting them. Since NICE was established in 1999, drug manufacturers have been invited to submit evidence on the health benefits and costs

of their drugs in comparison to the standard of care.[15] An evidence review group—generally a group of university based researchers contracted by NICE—then appraises the evidence in 'single technology appraisals' and produces independent estimates of health benefits, measured in QALYs.

Using data from NICE evidence review groups, we sought to better understand the incremental value of all new therapies assessed from 2010 to 2020. Although these data are used to inform public health decisions, we here present their implications from a patient's perspective. Specifically, we sought to identify disease areas where the greatest gains from novel therapies have occurred, and the differing average amounts of gain per drug for individual patients in each disease area.

MATERIALS AND METHODS

We identified all single technology appraisals of novel pharmaceuticals that were submitted to NICE between January 1st, 2010 and December 31st, 2020.[16] Data were extracted on May 1st, 2021. We excluded drug appraisals resulting in negative coverage decisions, appraisals for which no data were available because of termination, withdrawal, or reconsideration, and appraisals that addressed only cost-saving issues and lacked QALY data.

Two authors (TBP and DGJC) independently extracted QALY estimates from each drug's appraisal documents. Discordance was resolved by discussion with the last author (MMV). As per NICE guidance,[17] QALYs are calculated over the remainder lifetime of patients, and future health benefits are discounted at a 3.5% annual rate. We extracted these 'net present' values. When appraisal documents included multiple comparators, we extracted the QALY value that corresponded to the best alternative therapy. As a sensitivity analysis, in the case of multiple comparators, we also computed the added value compared with the next-best alternative. We disregarded cost, as we focused on health gains for individual patients and not on health care systems.

The evidence review group usually specified which of the modelled QALYs was its preferred estimate of health benefit (i.e., which modelling assumptions were deemed most appropriate to the review group). If the evidence review group did not clearly document their preference and this could not be determined after deliberation with the last author (MMV), we discarded the appraisal from our analysis. Although manufacturers frequently report the incremental cost-effectiveness ratio in cost (British pounds) per QALY, they are not required to disclose the individual components of this ratio. We therefore removed appraisals in which the manufacturer redacted all estimates of incremental QALYs (also see: Supplementary Material). A schematic overview of our appraisal selection and data extraction method is depicted in Figure 3.

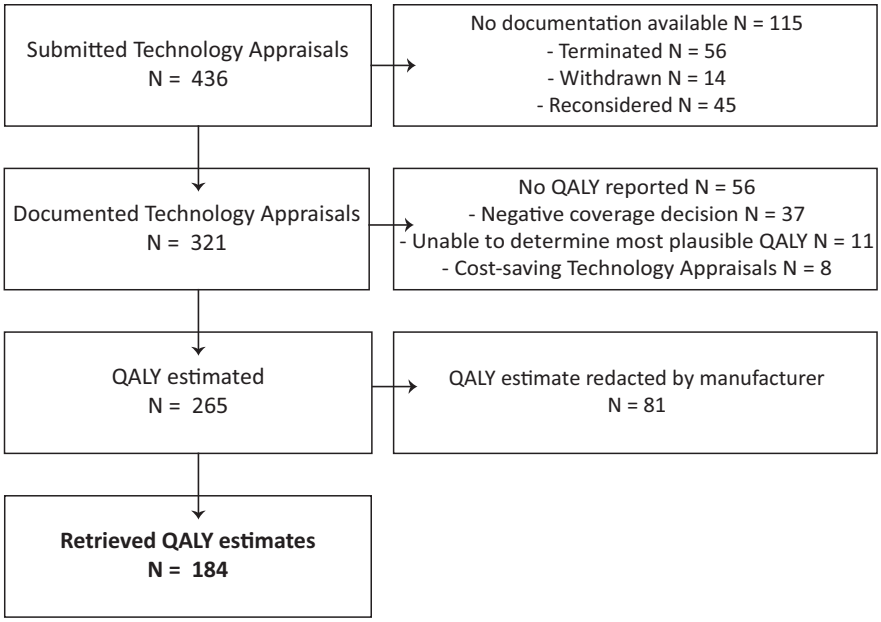


Figure 3: Flow diagram of the selection and retrieval of estimates of Quality-Adjusted Life Years (QALYs) from NICE technology appraisals between January 1st, 2010 and December 31st, 2020.

Each appraisal was categorized according to its medical discipline: cardiology, endocrinology, gastroenterology, hematology, neurology, oncology, ophthalmology, rheumatology, vascular medicine, infectious diseases and other (benign hematology, dermatology, internal medicine, nephrology, psychiatry, pulmonology, urology). Summary statistics were calculated and visualized in R version 4.0.5.

RESULTS

Between January 1st, 2010 and December 31st, 2020, 436 single technology appraisals were submitted to NICE associated with 212 drugs. No documentation was available for 115 appraisals, including 14 that were withdrawn, 56 that were terminated, and 45 that were later reconsidered or updated. Another 37 appraised drug-indication pairs received a negative reimbursement determination, meaning they were not considered a cost-effective use of NHS resources and thus did not become available to patients in the UK. An estimate of QALY gain could not be extracted in 19 appraisals, because QALYs were not reported in cost-saving appraisals or because the evidence review group did not specify its preferred estimate out of several reported outcomes. After these exclusions, 265 appraisals were available for evaluation, associated with 171 drugs. Of these appraisals, 81 had their incremental QALY estimates redacted (Supplementary Material),

which can occur at the company's request, leaving 184 appraisals associated with 129 drugs for inclusion in our data set (different appraisals can review the same drug for different indications).

Of the 184 drug-indication pairs,the median incremental QALY gain relative to the best alternative therapy was 0.27 QALY (interquartile range [IQR]: 0.07-0.73) (Figure 4). The highest median benefits were associated with drugs developed for medical disciplines such as hematology (0.70, IQR: 0.55-1.22), oncology (0.46, IQR: 0.20-0.88), and neurology (0.45, IQR: 0.13-1.15), and the lowest for drugs associated with medical disciplines such as vascular medicine (0.11, IQR: 0.01-0.19), ophthalmology (0.09, IQR: 0.04-0.22) and endocrinology (0.02, IQR: 0.01-0.06). Of note, QALY estimates were redacted in 26.7% of neurology, 28.6% of ophthalmology, 37.2% of oncology and 44.9% of hematology appraisals, whereas for vascular medicine and endocrinology, QALY estimates were available in all appraisals (also see Supplementary Material).

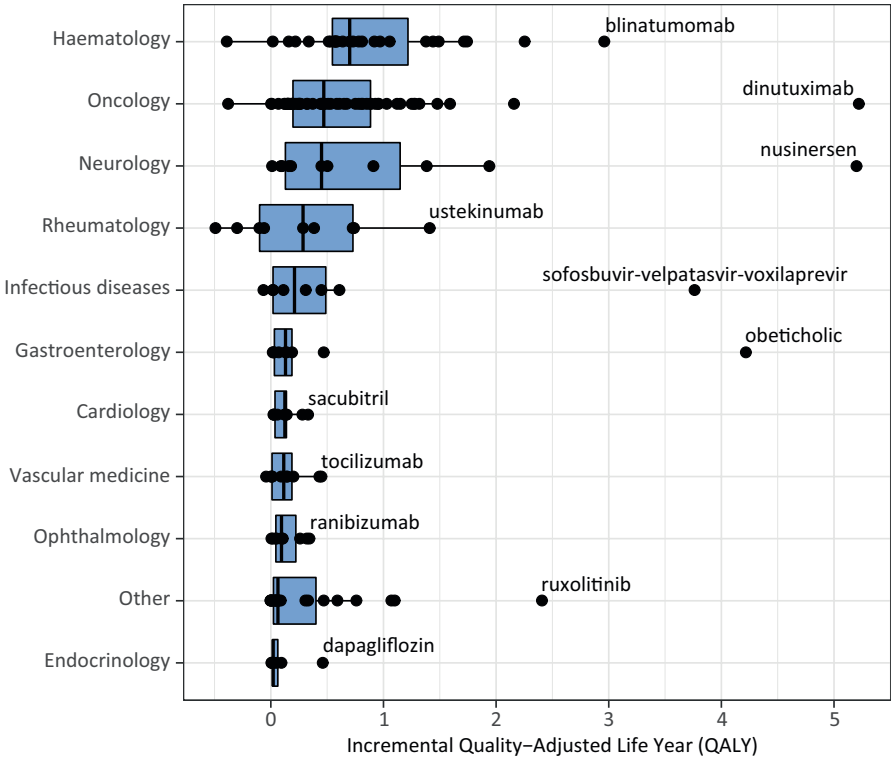


Figure 4: The added value of novel pharmaceuticals approved by NICE from 2010 to 2020. Display of the distribution (boxplot) of added value in Quality-Adjusted Life Years (QALYs) of novel pharmaceuticals per medical discipline that have received a positive coverage decision of NICE between January 1, 2010 and December 31, 2020, compared with their next-best alternative. Medical disciplines with fewer than eight appraisals were classified as 'Other'.

In our review period, eight (4.3%) positive coverage decisions were granted to drugs contributing more than the equivalent of two life years in perfect health. Both dinutuximab beta to treat neuroblastoma and nusinersen used to treat children with spinal muscular atrophy led patients to accumulate 5.2 incremental QALYs.

On the other hand, 50 (27%) drugs contributed no more than the equivalent of one month in perfect health over the best alternative therapeutic option (≤ 0.082 QALY) (Table 3). Eight drugs were estimated to provide lower QALY gains than their next best alternative. Government decision makers may nevertheless be willing to pay for such products thanks to the uncertainty around point estimates, together with strategic pricing by manufacturers. For example, one drug, venetoclax, was estimated to be inferior to its direct comparator (ibrutinib) in the treatment of chronic lymphocytic leukemia. Although this negative point estimate was considered most plausible by the evidence review group, there was still considerable uncertainty remaining as the group also provided higher estimates (an incremental benefit of 0.51 when idelalisib was the comparator) and lower estimates (-1.75 when treatment effects of venetoclax were assumed to be waning faster than expected) under varying assumptions. Venetoclax was offered at a lower price than ibrutinib, and NICE concluded that the new drug was likely a cost-effective use of NHS resources in the treatment of lymphocytic leukemia.[18]

Table 3: Pharmaceuticals that produced most and least incremental health benefit, ranked according to their added Quality-Adjusted Life Years (QALYs) extracted from NICE Technology Appraisals (TAs).

TA	Product	Disease	QALY	SPECIFICS
TOP-5 PHARMACEUTICALS WITH THE LARGEST INCREMENTAL HEALTH BENEFITS, COMPARED WITH THEIR NEXT-BEST ALTERNATIVE.				
TA538	dinutuximab beta	neuroblastoma	5.22	Dinutuximab beta for treating high-risk neuroblastoma in people aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplant, only if they have not already had anti-GD2 immunotherapy.
TA588	nusinersen	spinal muscular atrophy	5.20	Nusinersen for treating 5q spinal muscular atrophy (SMA) only if people have pre-symptomatic SMA, or SMA types 1, 2 or 3.
TA443	obeticholic	primary biliary cholangitis	4.22	Obeticholic acid for treating primary biliary cholangitis in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid.
TA507	sofosbuvir–velpatasvir–voxilaprevir	chronic hepatitis C	3.76	Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C in direct-acting antivirals experienced patients.
TA589	blinatumomab	acute lymphoblastic leukemia	2.96	Blinatumomab for treating Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukemia in adults with minimal residual disease (MRD) of at least 0.1%, only if the disease is in first complete remission.
TOP-5 PHARMACEUTICALS WITH THE SMALLEST INCREMENTAL HEALTH BENEFITS COMPARED WITH THEIR NEXT-BEST ALTERNATIVE.				
TA537	ixekizumab	psoriatic arthritis	-0.10	Ixekizumab (alone or with methotrexate) for treating active psoriatic arthritis in adults who have not responded to, or are ineligible for, a TNF-alpha inhibitor.
TA220	golimumab	psoriatic arthritis	-0.30	Golimumab for the treatment of active and progressive psoriatic arthritis.
TA512	tivozanib	renal cell carcinoma	-0.38	Tivozanib for treating advanced renal cell carcinoma in adults, only if they have had no previous treatment.
TA561	venetoclax	chronic lymphocytic leukemia	-0.39	Venetoclax (with rituximab) for treating chronic lymphocytic leukemia in adults who have had at least 1 previous therapy.
TA543	tofacitinib	psoriatic arthritis	-0.49	Tofacitinib (with methotrexate) for treating active psoriatic arthritis in adults who have not responded to, or are ineligible for, a TNF-alpha inhibitor.

When selecting the next-best drug as a comparator instead of the best available comparator, the median added value slightly increases (0.31, IQR: 0.09 – 0.73), suggesting our results are robust under these different choices of comparators.

DISCUSSION

Novel pharmaceuticals that became publicly available to patients in the NHS over the past eleven years and that were favorably evaluated by NICE contributed the net present equivalent of between three to four months of life in perfect health relative to the best alternative therapy. The added benefit varied greatly, including eight drugs that were inferior in some cases to its already-available counterpart, and two that provided the equivalent of over five years in perfect health. To our knowledge, this analysis is the first to compare the therapeutic value of drugs across diverse disease areas using QALYs extracted from independent cost-effectiveness analyses conducted through a standardized framework.

The largest benefits were observed in areas such as hematology or oncology, where drugs were shown to improve quality or duration of life by 0.70 and 0.46 QALY. Patients have least profited from pharmaceutical innovations in endocrinology and ophthalmology, where novel pharmaceuticals were associated with a median incremental benefit of 0.02 to 0.09 QALYs.

The nature of each treatment (curative, palliative, symptomatic, preventive) may impact the incremental QALY. For example, adult patients that have undergone total hip or knee replacements may be treated with apixaban (TA245) to prevent venous thromboembolism. When used for this indication, apixaban provides an incremental benefit of 0.0016 QALY over the standard of care (low-molecular-weight heparin), equivalent to an additional fourteen hours of life in perfect health. The very low benefit reflected estimates that one venous thromboembolism event would be prevented for every 110–250 patients treated prophylactically for ten days following surgery.[19–21] Although apixaban may prevent serious outcomes (death) in some patients, outcome heterogeneity led to the extremely low average incremental QALY.

QALY evaluations are necessarily based on the data available at the time of drug approval, which are in turn increasingly based on earlier-phase trials, but later-generated evidence often fails to confirm promising early results.[22] Furthermore, most (59%) drugs are now approved on the basis of surrogate endpoints,[23] such as progression free survival, which for purposes of QALY calculations are assumed to correlate with clinical outcomes such as increased survival. However, studies have shown that this correlation is often poor or fair, particularly in oncology.[24,25] Additionally, data on infrequent or longer-term harms cannot be known with certainty or incorporated in the appraisals, as these data only become apparent when the drug is available for broader use.

Furthermore, fitter patients are often recruited for clinical trial participation and the outcomes for more vulnerable patients are not known. Factors such as these could cause QALY values to be lower than NICE estimates suggest.

Three additional issues can also lead to overestimations in incremental therapeutic benefit. First, during the time it takes to plan and conduct a trial, approve a drug, and complete a cost-effectiveness assessment, the standard of care may have shifted, and the best available comparator may no longer provide the relevant baseline for comparison. Second, a drug may have different benefits for different indications, a factor of particular relevance when off-label use is widespread or where marketing authorization is granted for a population that is broader than the tested population. Third, trials may be designed to demonstrate incremental benefit even when available treatments might demonstrate similar efficacy if tested with a different trial design.

Our findings should be interpreted with caution and cannot easily be interpreted from a population health perspective, as drug-indication pairs may be reimbursed within some health systems only for specific patient populations. For example, some of these large incremental benefits mainly occur for drugs that were not considered cost-effective in earlier lines of therapy – but when all prior therapies fail, these drugs are estimated to provide substantial benefit. From the examples in Table 3, sofosbuvir-velpatasvir-voxilaprevir is estimated to generate 3.76 incremental QALYs for patients who have previously been treated with direct-acting antivirals. However, the Marketing Authorization has been granted to treat patients regardless of cirrhosis status and treatment history. These benefits must be seen in this larger context.

Our study has a few limitations. First, our analysis was restricted to data presented to NICE of drugs that subsequently obtained a positive coverage decision, excluding medicine that may be accessed via private health insurance. Therefore, drugs in our review are a subset of the drugs covered in other analyses of medication approved by the FDA or EMA, a subset that is likely to be associated with higher QALY estimates than the average new drug. Not all FDA-approved drugs are subsequently approved by the EMA, and not all EMA-approved drugs are assessed by NICE. A recent assessment of oncology drugs approved via the FDA's accelerated approval pathway demonstrated that only half (48%, 45/93) of drug-indication pairs subsequently became reimbursed within the English NHS, suggesting their therapeutic benefit was not sufficiently important or well established in relation to the associated cost to receive a positive reimbursement decision.[26]

Second, we could not retrieve all estimates of health benefit as some were concealed by the manufacturer, the implications of which are unclear. It seems some companies maintain a policy of not disclosing QALY figures for any indications or drugs, whereas other companies consistently

provide full disclosure. The desire to maintain in confidence the incremental cost of their treatment, which would implicitly be made evident if both cost/benefit ratios and QALY values were simultaneously disclosed, may be the driving force behind redactions. In the Supplementary Material, we provide examples where we could retrieve estimates due to ineffective redaction. We also list the number of redacted estimates by disease area. The rates of redaction in oncology (37.2%) and hematology (44.9%), compared with other disease areas (such as cardiology, vascular medicine, endocrinology) where none of the values were redacted, may either represent the unwillingness to disclose high drug prices in these indications,[27] or the unwillingness to disclose low benefits, the latter of which may make average QALY figures appear larger than they are for these disease areas. For withdrawn or terminated appraisals, no detailed information is available to the public on cost or QALYs. Although speculative, it is unlikely these appraisals discussed drugs that were cheaper and more effective than the current standard of care.

Third, QALY estimates of individual products are sensitive to the choice of relevant comparator. Our results, however, show that the choice of comparator does not significantly affect the overall estimated QALY gain in our dataset. Alternatively, one may not be interested in the overall population, but only in specific (sub)populations reported in the appraisal documentation. This may give more specific estimates for individual patients but impedes the comparison of drugs across diseases.

Fourth, estimates of median incremental QALY for each drug are associated with varying degrees of uncertainty. Although we have extracted the 'preferred' estimate from the evidence review group, the variance of these estimates is not routinely reported. Furthermore, distinct preferences in modelling choices, may result in substantial differences in benefit estimates.

Our findings provide insight into the relative benefits of new pharmaceuticals across therapeutic areas. Additional health gains may be hindered by the difficulty of developing novel drugs for specific diseases, perhaps because major improvements have already been generated prior to our review period,[28,29] or because scientific breakthroughs have not yet occurred. QALYs are a useful tool for comparison, but the measure omits important health-related variables, such as the extent to which a patient remains unable to live out a 'normal' life expectancy or achieve complete health. Other factors, such as lack of fundamental understanding of disease pathologies,[30,31] or the abundance or absence of sufficient research funding may also limit health gains.[32] Our figures evaluate the net present health-related benefits of drugs that are considered cost-effective by NICE over the past decade. In combination with indices measuring health needs, such as the Global Burden of Disease,[33] as well as cost-effectiveness/cost-saving data of novel drugs that might produce similar QALYs as already available therapies, our findings can help provide context for the allocation of research funding and thereby shape health policy.

Eight drugs improved life by more than two incremental QALYs, which may justify their superlative epithets of 'ground-breaking' or 'game-changing'.[2] Half of the drugs in our study were likely to improve life by the equivalent of three to four months in perfect health, and 84.8% of novel drugs did not add more than one such year. Unfortunately, 25% of appraisals have covered drugs that contributed the equivalent of no more than one month in perfect health, and 23 (12.5%) drug-indication pairs were estimated to add several hours to just a week of perfect health. For example, eluxadoline for prevention of diarrhea and abdominal pain in patients with irritable bowel syndrome yielded a total QALY gain of 0.015—equivalent to 5.5 days in perfect health—compared with placebo. Given the uncertainty around cost-effectiveness estimates—models that require ample assumptions and extrapolations over lifetime horizons can hardly be expected to accurately forecast a week of health gained—drafting extensive cost-effectiveness reports in these situations is not likely to be a cost-effective use of time.

Drugs that have little health benefit relative to the best alternative may still promote price competition and thereby free funds for other public health initiatives or treatments. To avoid wasting public resources in needless evaluations, guideline committees could determine a threshold of incremental benefit that is clinically relevant to each disease area.[34] Drugs that do not pass this threshold based on early assessments of their value should be rejected without a full evaluation unless they are offered at lower cost.

Patients and physicians can use the QALY data presented here to put the effectiveness of treatments in perspective. The frequently employed metric of 'number needed to treat' provides important information about the effectiveness of drugs on the principal disease-specific outcome. For example, the efficacy of eluxadoline could be described in terms of the number of patients that would need to be treated three months to avoid one episode of abdominal pain or diarrhea, in this case between eight and 33 patients over three months.[35] Metrics such as this, however, do not account for adverse events. Using the incremental QALY estimate that integrates gains and losses into a single measure (for eluxadoline, 0.015), it is possible to calculate that 67 patients would need to be treated over their lifetime horizons to gain the equivalent of one year in perfect health. As such, the QALY provides an estimate of both duration and quality of life, which are arguably the two most important factors from the perspective of a patient.

Conclusions

Novel pharmaceuticals that received a positive coverage decision by NICE from 2010 to 2020 provided patients with an average of 0.27 additional QALYs over the best alternative therapy, the equivalent of three to four additional months of life in perfect health. One in four drugs does not improve quality and quantity of life by more than one month, and incremental benefit varies

greatly across disease areas and compounds. Several novel drugs do not provide additional QALY gains over available therapies, but if offered at a lower price could still be of interest from a public cost-saving perspective even if not from the patient's perspective. Providing transparent information on the added value of novel therapies enables patients and physicians to have reasonable expectations about the average net benefits of therapies at their disposal. Objectively evaluating the benefits contributed by novel pharmaceuticals provides insight not only into whether a given drug is worth its price once approved, but also into the therapeutic return on investment reaped by society from the substantial public and private sums expended on research and development. Finally, these figures provide a benchmark for future innovations.

SUPPLEMENTARY MATERIAL

This Supplementary Material provides more background information regarding the redaction of estimates of cost, Quality-Adjusted Life Years (QALYs) and Incremental Cost-Effectiveness Ratio's (ICERs) available in Technology Appraisals (TAs) as available from the National Institute of Care and Excellence (NICE) in the United Kingdom.

Part A: Overview of redacted appraisals

Supplementary table 1: Overview of redacted technology appraisals by disease area

	Estimate Redacted		
Disease area	**Yes, N = 81[1]**	**No, N = 184[1]**	**Overall, N = 265**
Oncology	35 (37%)	59 (63%)	94
Hematology	22 (45%)	27 (55%)	49
Neurology	4 (27%)	11 (73%)	15
Ophthalmology	4 (29%)	10 (71%)	14
Rheumatology	5 (36%)	9 (64%)	14
Gastroenterology	2 (18%)	9 (82%)	11
Cardiology	0 (0%)	10 (100%)	10
Dermatology	3 (30%)	7 (70%)	10
Vascular medicine	0 (0%)	10 (100%)	10
Endocrinology	0 (0%)	8 (100%)	8
Infectious diseases	0 (0%)	8 (100%)	8
Pulmonology	2 (29%)	5 (71%)	7
Benign hematology	1 (25%)	3 (75%)	4
Psychiatry	0 (0%)	4 (100%)	4
Internal medicine	2 (67%)	1 (33%)	3
Nephrology	0 (0%)	2 (100%)	2
Urology	1 (50%)	1 (50%)	2

[1]n (%)

Part B: Example of various redaction strategies

1 Complete redaction

Table 28: Scenario analyses for prolonged post-treatment overall survival benefit (including ERG corrections)

Extension	Total			Incremental			ICER (£/QALY)
Treatment	*Costs*	*QALYs*	*Life years*	*Costs*	*QALYs*	*Life years*	
Base case							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+1 month							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+2 months							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+3 months							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
−1 month							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

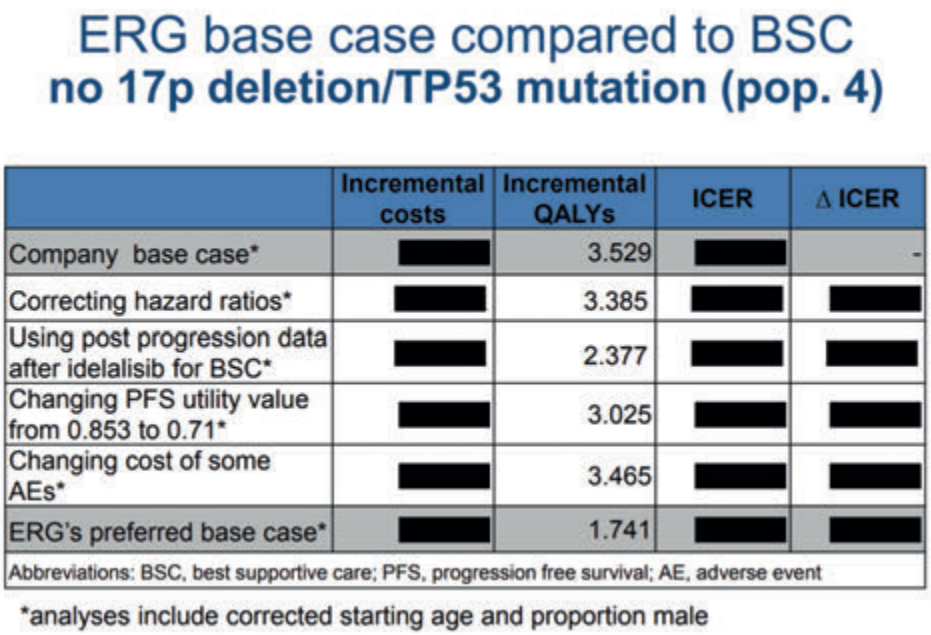
Supplementary Figure 1: Completely redacted estimates (ICER, QALY, cost) from TA401: Bosutinib for previously treated chronic myeloid leukaemia. Table from Evidence Review Group Report.

Table 62. Deterministic results using the PAS for dacomitinib and the list prices for the comparators

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained					

Supplementary Figure 2: Completely redacted estimates (ICER, QALY, cost) from TA595: Dacomitinib for untreated EGFR mutation-positive non-small-cell lung cancer. Table from Evidence Review Group Report.

2 Incomplete redaction



ERG base case compared to BSC
no 17p deletion/TP53 mutation (pop. 4)

	Incremental costs	Incremental QALYs	ICER	Δ ICER
Company base case*	[redacted]	3.529	[redacted]	-
Correcting hazard ratios*	[redacted]	3.385	[redacted]	[redacted]
Using post progression data after idelalisib for BSC*	[redacted]	2.377	[redacted]	[redacted]
Changing PFS utility value from 0.853 to 0.71*	[redacted]	3.025	[redacted]	[redacted]
Changing cost of some AEs*	[redacted]	3.465	[redacted]	[redacted]
ERG's preferred base case*	[redacted]	1.741	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; PFS, progression free survival; AE, adverse event

*analyses include corrected starting age and proportion male

Supplementary Figure 3: Redacted estimates (ICER, cost) from TA487: Venetoclax for treating chronic lymphocytic leukaemia. Table from the Public Committee Slides Appraisal Consultation.

Table 64: Exploratory Analysis 4 – ERG-preferred base case

Probabilistic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£61,219**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£61,050**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Supplementary Figure 4: Redacted estimates (QALY, cost) from TA491: Ibrutinib for treating Waldenström macroglobulinemia. Table from Evidence Review Group Report.

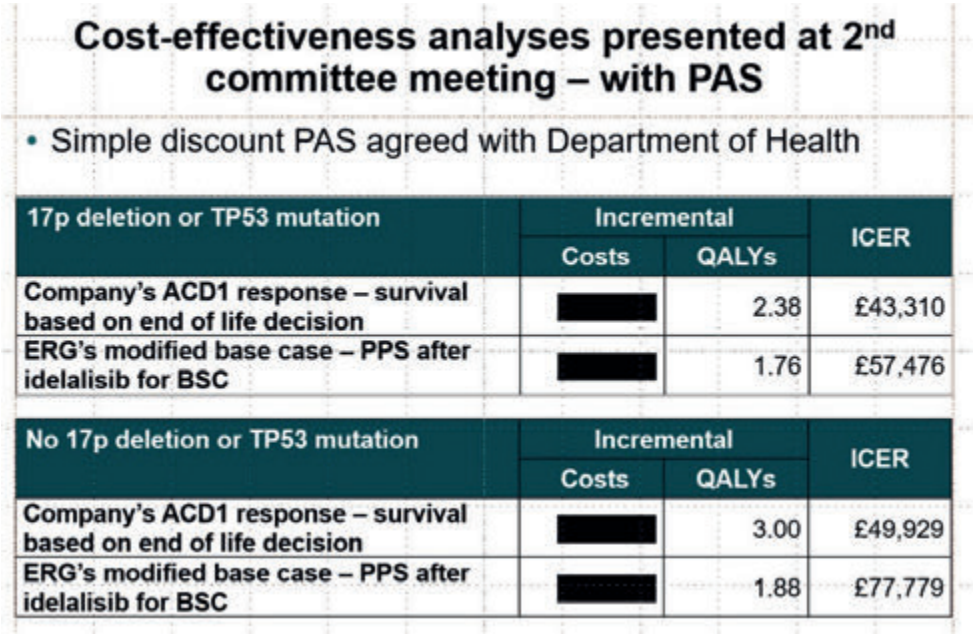
3 Erroneous redaction

Table 5-1 Effect of corrections and amendments made by ERG to the manufacturer's model for the base case analysis (paclitaxel/carboplatin as comparator) over 6 years

	Gefitinib / carboplatin		Paclitaxel / carboplatin		Incremental		ICER	Changes (from 6 year horizon base case)		
Model amendment	Costs	QALYs	Costs	QALYs	Costs	QALYs	(£/QALY)	Costs	QALYs	ICER
Submitted base case	[redacted]	**1.1110**	**£27,902**	**0.9235**	**£3,637**	**0.1874**	**£19,402**			
Base case with 6 year horizon	[redacted]	**1.1110**	**£27,947**	**0.9235**	**£3,751**	**0.1874**	**£20,010**			
Amend 1st line CTX costs	[redacted]	1.1110	£24,563	0.9235	£7,135	0.1874	£38,063	+£3,498	0.0000	+£18,054
Reduced cycles of CTX	[redacted]	1.1110	£25,527	0.9270	£6,170	0.1839	£33,544	+£2,420	-0.0035	+£13,535
Revise OS models	[redacted]	1.2219	£32,985	1.0834	£2,268	0.1384	£16,381	-£1,483	-0.0490	-£3,628
Revise PFS models	[redacted]	1.0923	£28,149	0.9181	£4,989	0.1741	£28,651	+£1,238	-0.0133	+£8,641
IPASS PFS HR (not MA)	[redacted]	1.1020	£29,947	0.9235	£4,439	0.1785	£24,867	+£688	-0.0089	+£4,857
Revise discounting method	[redacted]	1.1284	£28,337	0.9378	£3,680	0.1906	£19,311	-£71	+0.0032	-£699
Omit GCSF prophylaxis	[redacted]	1.1110	£27,669	0.9235	£4,029	0.1874	£21,493	+£278	0.0000	+£1,483
Continuity correction	[redacted]	1.1110	£28,426	0.9235	£3,252	0.1874	£17,350	-£499	0.0000	-£2,660
Correct misaligned cycles	[redacted]	1.1110	£27,947	0.9235	£3,752	0.1874	£20,017	+£1	0.0000	+£7
Correct 2nd line CTX costs	[redacted]	1.1110	£25,213	0.9235	£3,975	0.1874	£21,204	+£224	0.0000	+£1,194
CTX treatment exposure	[redacted]	1.1110	£26,931	0.9235	£4,766	0.1874	£25,427	+£1,015	0.0000	+£5,417
Combined effect of all changes	[redacted]	**1.2223**	**£24,574**	**1.0988**	**£8,746**	**0.1235**	**£70,822**	**+£4,995**	**-0.0639**	**+£50,812**

ICER= incremental cost effectiveness ratio; QALY=quality adjusted life year; CTX= chemotherapy; OS= overall survival; PFS= progression free survival; granulocyte colony stimulating factor; HR=hazard ratio; MA= meta-analysis

Supplementary Figure 5: Erroneous redaction of cost only from TA192: Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. Table from the Advisory Committee Decision Pre-meeting Briefing



Supplementary Figure 6: Erroneous redaction of cost only from TA487: Venetoclax for treating chronic lymphocytic leukaemia. Table from the Public Committee Slides Final Appraisal Determination.

EPILOGUE

Based on our research, we conclude that the benefits of drugs under development is highly variable. If there is benefit at all, the magnitude of that benefit equally variable. Some drugs provide marginal improvements, while other drugs may cure patients from their illnesses.

Patients that opt to access drugs in development through expanded access do so in the hope of accessing life-saving drugs. As we have concluded in our research, the majority of drugs under development cannot live up to that expectation. Physicians and patients could be misled by overconfident positive results presented both by physician-researchers and medical writers, and in publicly accessible channels such as news media and social media. It is crucial to ensure that patients are adequately informed of the risks and benefits of accessing drugs through expanded access.

However, this part is only a proxy for assessing the value of expanded access. In theory, if expanded access only occurred to the most effective drugs, the average 'effectiveness' of drugs is not a good estimate of the added value of expanded access. Unfortunately, actual numbers of patient access to individual drugs are confidential and known only to regulators and drug companies. Nevertheless, our paper in Part II 'Results from expanded access programs: a review of academic literature' will highlight that the scientific dissemination of expanded access programs does show disproportionate access to 'successful' drugs, as the most frequently described drugs in expanded access publications are nivolumab, ipilimumab, gefitinib, sofosbuvir, and sunitinib which are all regulatory approved drugs with substantial clinical benefit. Moreover, as can be see in Figure 1 in the Prelude, the (group) compassionate use programs initiated in the Netherlands were aimed at highly effective drugs, such as blinatumomab, which in our analysis revealed the highest QALY gain among all hematology drugs (Figure 4).

Similarly, previous research has shown that expanded access increases as data accumulates when drugs advance through the stages of clinical development.[3] Regulators are increasingly willing to allow access to experimental drugs as more data becomes available, physician may feel more confident in prescribing later-stage drugs, and medical companies see less risk in providing access to drugs where substantial data on safety and efficacy has been obtained. This natural process decreases the chances that patient would access ineffective drugs, and positively effects clinical merit of expanded access for individual patients.

While it is crucial not to overstate the clinical value of drugs in development and expanded access itself, there may still be value in expanded access programs that go beyond individual patient perspectives and provide collective benefits. For example, patients can contribute to scientific research through the generation of data within expanded access programs.

In upcoming chapters, we will explore the potential value of data generated by expanded access programs through the lens of regulators, reimbursement bodies, and researchers. We will explore the often overlooked 'research' aspect of the expanded access 'treatment' pathway.

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PART II

The usage of expanded access data

PROLOGUE

In this part, we aim to establish a systematic understanding of the use of data from expanded access programs. Inspired by anecdotal evidence reports, such as the Reagan-Udall Foundation report,[1] which mentioned the inclusion of data from expanded access program to support clinical efficacy, we started wondering how often data from expanded access programs were included in regulatory filings. We were primarily interested in the efficacy from these programs – as safety reporting is both obligatory and there has been prior scholarship devoted to exploring the implications of expanded access safety issues on clinical development. Hence, we aimed to first find out how many regulatory filings included data from expanded access programs to support efficacy.

Traditional regulatory analysis involves a manual review of each drug approval, a process that would be time-consuming and error-prone for the vast amount of data involved. To give the reader a sense of the magnitude of this issue: the FDA typically employs various types of reviews: a summary review, a medical review, a chemistry review, a pharmacology review, a statistical review, a clinical pharmacology biopharmaceutics review and a microbiology review, to name a few. Scanning these documents for decades of drug approvals would be an onerous, inefficient, and fallible process. Furthermore, given only the handful of examples mentioned in the Reagan-Udall Report, we might be looking for a needle in a haystack. Similar issues pertain to the EMA, where thousands of pages of information are available per drug approval.

We therefore designed an algorithmic approach that automatically downloaded all available documents from the FDA and EMA websites, and then scanned all documents for any terms relevant to expanded access, 'Compassionate Use', 'Expanded Access', 'Early Access', 'Single-patient IND', and all possible spellings thereof. In this way, we could reasonably argue that documents that did not include such a term were unlikely to have employed data from expanded access programs, and we only manually had to search through the documents that appeared in our algorithm.

We reused this technique several times. We could not only analyze FDA or EMA documents, but also approvals from other jurisdictions. And there was no reason to limit ourselves to regulators – we extended our work to analyze whether reimbursement decisions employed expanded access data. Lastly, we did a thorough systematic review of all scholar publications that disseminated results of expanded access drugs. Here, we made use of old-fashioned, authentic independent review techniques.

Throughout this chapter, we show that the analysis of vast amounts of health policy documents

can be facilitated through modern techniques. We use these partly automated techniques in three different papers in this chapter:

1. Identifying the expanded access data regulatory usage of FDA and EMA on clinical efficacy.
2. Understanding how expanded access data could support reimbursement decisions made in the United Kingdom.
3. Undertaking a large systematic review of all PubMed-index peer-reviewed papers that disseminated original research on expanded access drugs.

The code to replicate these analyses can be found on GitHub of the first author[1]. To make the results available to a broader public, we created small explainer videos and animations to illustrate our methods and results. These animations can be directly accessed through the QR-codes located under the abstracts of the individual chapters.

1 https://github.com/TobiasPolak

CHAPTER 5

Expanded access as a source of real-world data: An overview of FDA and EMA approvals

Polak TB, van Rosmalen J, Uyl-de Groot CA.
Br J Clin Pharmacol. 2020 Sep;86(9):1819-1826.

ABSTRACT

Aims To identify, characterize, and compare all Food and Drug Administration (FDA) and European Medicines Agency (EMA) approvals that included real-world data on efficacy from expanded access programs.

Methods Cross-sectional study of FDA (1955-2018) and EMA (1995-2018) regulatory approval documentation. We automated searching for terms related to expanded access in 22,506 documents using machine learning techniques. We included all approvals where expanded access terms appeared in the regulatory documentation. Our main outcome was the inclusion of expanded access data as evidence of clinical efficacy. Characterization was based on approval date, disease area, orphan designation and whether the evidence was supportive or pivotal.

Results Expanded access terms appeared in 693 out of 22,506 (3.1%) documents, which referenced 187 approvals. For 39 approvals, data from expanded access programs were used to inform on clinical efficacy. The yearly number of approvals with expanded access data increased from 1.25 for 1993-2013 to 4.6 from 2014-2018. In 13 cases, these programs formed the main evidence for approval. Of these, patients in expanded access programs formed over half (median 71%, IQR: 34 - 100) of the total patient population available for efficacy evaluation. Almost all (12/13) approvals were granted orphan designation. In 8/13, there were differences between regulators in approval status and valuation of evidence. Strikingly, four treatments were granted approval based solely on efficacy from expanded access.

Conclusions Sponsors and regulators increasingly include real-world data from expanded access programs in the efficacy profile of a treatment. The indications of the approved treatments are characterized by orphan designation and high unmet medical need.

INTRODUCTION

Patients suffering from seriously debilitating or life-threatening conditions who are not eligible for further treatments or any clinical trials, may resort to 'expanded access': pre-approval access to investigational treatments. Expanded access, also known as early access, pre-approval access or compassionate use,[2] is the formal regulation adopted by the Food and Drug Administration (FDA) in 1987,[3] propelled by the HIV/AIDS crisis. In the United States (US) the FDA regulates this process of formalized non-clinical trial access while in the European Union (EU) the responsibility lies with individual member states.[4] The exact conditions, types (single patient, group, protocolized, emergency) and definitions of expanded access vary between member states.[5] The numbers of requests for expanded access are growing and state and federal legislation, such as Right-to-Try laws in the US,[6] stress the need and interest of patients in having earlier access to medicines that are still under clinical investigation.

Also of interest, and closely related to expanded access, is the field of real-world data (RWD). RWD are information on health care that is derived from multiple sources outside typical clinical research settings.[7] Recent publications and regulatory frameworks have boosted the promise of RWD.[8–10] It can come in many forms and shapes, such as electronic health records, social media or claims databases.

Expanded access programs are generally considered to be a source of RWD.[1] Historically though, expanded access programs were only deemed fit for treatment and not for research. Although the primary purpose of expanded access is treatment, scholars have argued that there is a moral obligation to collect outcome data in all cases where patients are treated with investigational medicine.[11–13] The debate on combining data collection and expanded access has substantially increased,[14–16] with FDA-officials confirming beginning 2018 their willingness to review data from expanded access programs to support drug applications.[11]

Considering the increasing interest in both expanded access and RWD, the question arises whether alternative ways of access to novel treatments can provide clinical information and impact regulatory decision making. In this research, we systematically assess the role of RWD from expanded access programs in the regulatory approval process of the FDA and the European Medicines Agency (EMA), comparing and characterizing all approvals that utilize RWD on efficacy from expanded access programs.

METHOD

In the US, the FDA oversees both expanded access programs and marketing authorizations. In the EU, expanded access is supervised by individual member states, whereas marketing authorizations

are granted by the EMA via the centralized procedure. Therefore, to obtain an overview of whether data from expanded access programs were used for submissions, we downloaded the Drugs@FDA database and the EMA medicines overview on May 1st 2019. [17,18] For the FDA database, we downloaded the application documents (labels and reviews) associated with all approvals available in the database. Next to that, we retrieved documents from the drug approval packages sites. For the EMA, for each approved drug, we saved the scientific discussion, label and/or public assessment report that are listed in the database. Figure 1 gives a schematic overview of our method.

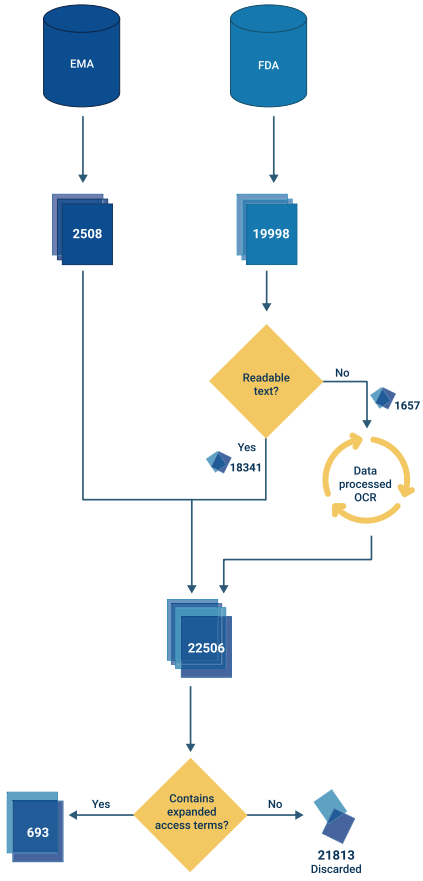

Figure 1: Flowchart of automated candidate search. We searched through all FDA and EMA documentation for expanded-access related terms[2]. When these terms appear, the document is considered a candidate. For scanned files, optical character recognition (OCR) was used.

2 'compassionate use', 'expanded access', 'early access', 'pre-approval access', 'named-patient' and 'managed access'

As some of the FDA documents are scanned files, we first performed optical character recognition (OCR) using Google's Tesseract engine,[19] to extract text from the scans, and subsequently process the extracted text .

To find candidate documents, i.e., documents that mention 'expanded access', we searched for the related terms: 'compassionate use', 'expanded access', 'early access', 'pre-approval access', 'named-patient' and 'managed access'. We expected these terms to appear if the data from an associated expanded access program were used in the submission package. When at least one of these terms appeared in the document, the associated submission package possibly included expanded access data for the approval. Therefore, we assessed these 'candidates' manually to determine whether data from expanded access were used in a supportive/pivotal manner, or whether the mention of EA-related terms was not in support of efficacy. The manual assessment was performed by T.B.P. and in case of doubt discussed with C.A.U.-d.G.

As all (pre-approval) data concerning patient safety are reported for purposes of pharmacovigilance, we focused on data from efficacy. Patients in expanded access programs are never randomized, and the absence of a direct control group makes it challenging to draw sound conclusions on efficacy. Nonetheless, this makes it even more attractive to understand the reasons that led to acceptance of expanded access programs as source of evidence.

Duplicates are removed from our data set. Duplication in this sense occurs when an approved treatment consists of multiple (recurring) compounds and the underlying data is duplicated. If no new data from expanded access were used, we removed such duplicates.

To determine whether expanded access data were included in the clinical efficacy profile, we followed two criteria. First, the data from the expanded access program must have been mentioned under the section 'clinical efficacy' in the medical/summary review (FDA) or scientific discussion/public assessment report (EMA). In addition, we studied the impact of the evidence. If the expanded access data were mentioned under the 'pivotal/main' studies, we considered the data to have a 'pivotal' (P) level of evidence. If not, we labeled the evidence as 'supportive' (S). For all candidate documents, we considered related approved treatment. Figure 2 illustrates our review procedure.

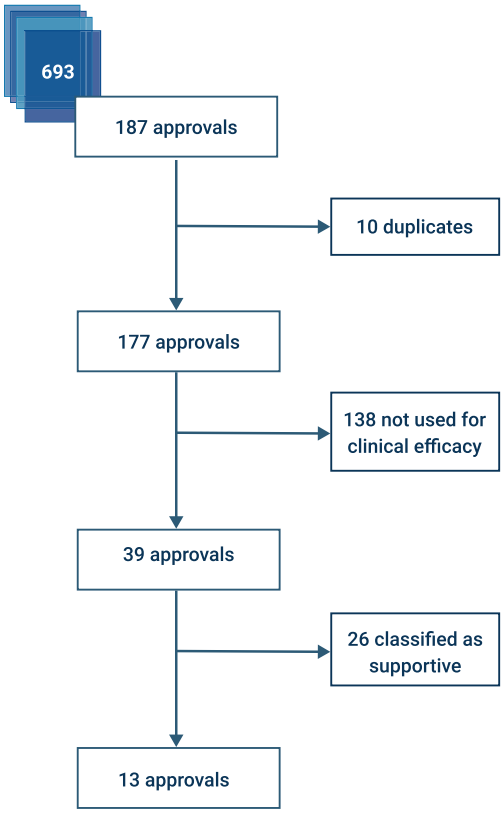

Figure 2: Flowchart of review process. We manually reviewed and deduplicated 187 approvals related to the candidate documents. All approvals that used expanded access (n=39) to support clinical efficacy were analyzed. For 13 approvals, the evidence from expanded access was the pivotal source of evidence.

Finally, we further inspected the group of approvals that included RWD from expanded access programs in terms of disease areas, orphan designation, timing of marketing approval and the number of patients in the expanded access programs relative (n_{EA}) to the total number of patients (N) in the trials. We used descriptive statistics to describe our data set. To compare our subset of approvals to regular approvals with respect to the number of orphan designations, we used chi-square tests with a two-sided significance level of 0.05. To detect a trend over time in the yearly numbers of approvals, we used a Spearman rank correlation test with a two-sided significance level of 0.05.

RESULTS

In total, 693 out of 22,506 scanned documents contained terms related to EA. The number of documents is skewed between agencies (2,508 EMA, 19,998 FDA), but this is mainly due to the nature of documentation. The FDA database distinguishes between medical reviews, chemistry reviews, pharmacology reviews, microbiology reviews, statistical review summary reviews and even all version updates thereof. The EMA merges the content of reviews in public assessment reports and scientific discussions. These 693 documents referenced 187 unique drug approvals, 126 from the FDA and 93 from the EMA (32 overlap). The FDA database contains documentation dating back to 1955. The first EMA documentation has been available since 1995.

As a first step, we removed ten duplicates, leaving 177 approvals. For example, the safety profile of tenofovir disoproxil mentions a 'compassionate use program'.[20] This is repeated in all documentation regarding highly active antiretroviral therapy in the treatment of HIV that tenofovir disoproxil is part of.

Second, we determined whether data from expanded access programs were used to back the profile of clinical efficacy of the treatment. This was the case in 22% (39/177) of all approvals. The FDA considered efficacy data in 25 cases, the EMA in 24 (10 overlapped). Interestingly, nearly three quarter (29/39) of these drugs were granted orphan designation. We encountered the first use of RWD from expanded access in 1993. From 1993 to 2013, the average number of approvals that included expanded access efficacy data per year was 1.24 (SD 1.09) versus 4.6 (SD 1.14) from 2014-2018. We observe a clear increase over the years with a Spearman correlation of 0.40 ($p = 0.042$). Figure 3 shows the distribution of these approvals by the EMA and the FDA, alongside their level of evidence, in a Venn diagram. Figure 4 displays the date of marketing authorization for these approvals.

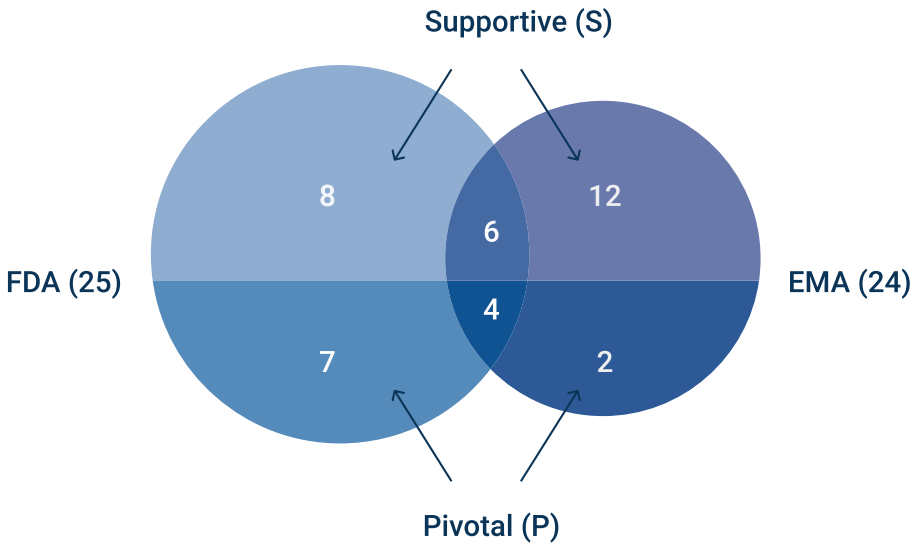

Figure 3: Venn-diagram of approvals where the FDA and or the EMA relied on data from expanded access programs to form the clinical efficacy profile. The level of evidence associated with these data by either regulators could be pivotal or supportive.

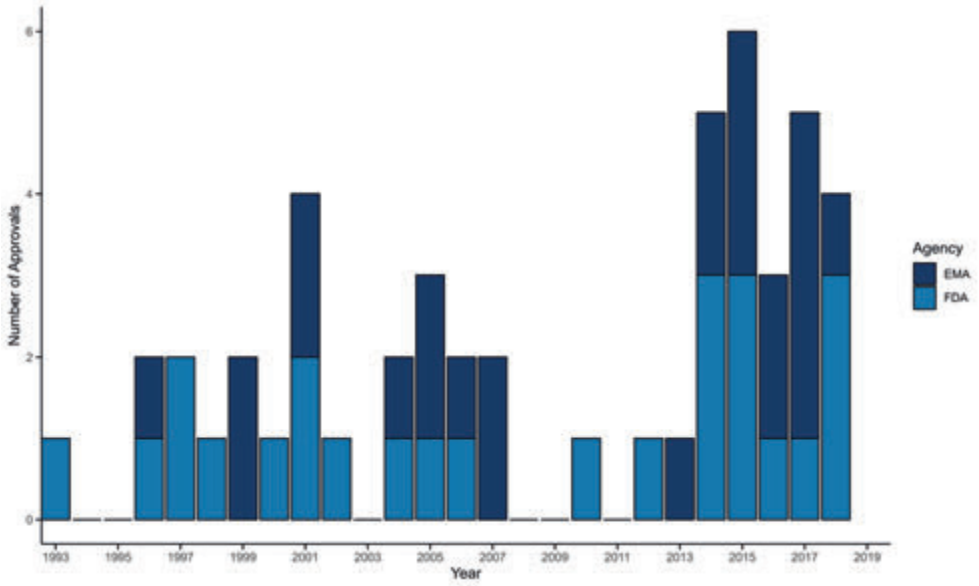

Figure 4: Bar chart of dates of marketing authorization of 25 FDA and 24 EMA approvals that relied on real-world data from expanded access for the clinical efficacy profile.

Expanded Access as pivotal evidence

We further investigate the approvals where RWD from expanded access programs played a pivotal role. This was the case in one third (13/ 39) of the group mentioned in the previous paragraph. Table 1 gives an overview of these approvals. Twelve out of 13 received orphan designation. This is significantly higher if we compare it to regular approvals. For example, EMA assigned orphan designation to 134 out of 1,111 all-time approved drugs versus 12 out of 13 drugs in the pivotal group ($p<0.0001$). If we characterize by indication, just under half of the approvals (6/13) concerned treatments for metabolic disorders. The remainder are divided between hemato-oncology (three indications), infectious diseases (two indications) and overdosing (two indications), all covering areas of high unmet medical need.

The median ratio of patients from expanded access programs to the total patient population ($n_{expanded\ access}$/ N) that pivotally reinforced the efficacy profile was 71% (IQR: 34 – 100). In absolute terms, this varies from only two (vestronidase alfa) up to 558 patients (lutetium oxodotreotride). Albeit small, the former two patients formed 12% (2/17) of the total patient population in pivotal studies. On the other hand, 558 patients comprised 71% (558/787) of the total patient population, meaning that almost three quarters of the patient population was treated under expanded access programs. Although 558 is the largest number of patients we observed in the pivotal group, we have encountered expanded access programs containing more than 13,000 patients (stavudine) that provided information on efficacy with a supportive level of evidence.

Table 1: Overview of all FDA and EMA approvals that rely in a pivotal way on real-world data from expanded access programs.

Generic name	Indication	FDA[3]	EMA	Studies[4]	N_{EA}/N[5]
amphotericin B	fungal infections	1997	N	10 CT (n=2,038), 1 EA (n=133)	0.06 (133/2,171)
anagrelide	essential thrombocythemia	1997	2004	2 SACT (n=35 + 254), 1EA (n=245)	0.45 (245/538)
cholic acid	inborn errors of bile acid metabolism	2015	2015	2 EA (n=63+22)	1.00 (85/85)
clarithromycin	Mycobacterium avium complex	1993	N[6]	1 RCT (n=154), 1 SACT (n=25), 1 EA (n=469)	0.72 (469/648)
dinutuximab β	neuroblastoma	N[7]	2017	1 RCT (n=370), 1 SACT (n=44), 1 EA (n=54)	0.12 (54/468)
fish oil triglycerides	parenteral nutrition-associated cholestasis	2018	N	1 SACT (n=144), 1 EA (n=37)	0.20 (37/181)
glucarpidase	elevated methotrexate levels	2012	W	1 SACT (n=147), 1 EA (n=22)	0.13 (22/169)
lutetium oxodotreotide	neuroendocrine tumors	2018	2017	1 RCT (n=229), 1 EA (n=558)	0.71 (558/787)
nitisinone	tyrosinemias	2002	2005	1 EA (n=207)	1.00 (207/207)
sodium phenylacetate/benzoate	acute hyperammonemia in urea cycle disorders	2005	N	1 EA (n=316)	1.00 (316/316)
uridine triacetate	fluorouracil or capecitabine overdose	2015	N	2 EA (n=75+60)	1.00 (135/135)
velmanase α	alpha-mannosidosis	N	2018	1 RCT (n=25), 1 EA (n=35)	0.58 (35/60)
vestronidase α	mucopolysaccharidosis VII	2017	2018	2 SACT (n=3+12), 1 EA (n=2)[8]	0.12 (2/17)

3 Year of EMA/FDA approval (if applicable). W: Withdrawn, N: Not approved.
4 Main studies that provided information on efficacy. SACT = single arm clinical trial, EA = expanded access, (R)CT = (randomized) controlled trial.
5 Ratio of patients in expanded access (nEa) to total number of patients in main studies (N)
6 Clarithromycin is approved in individual member states, before the introduction of the centralized procedure.
7 Dinutuximab α is marketed in the US (Unituxin) but not anymore in the EU (replaced by β). As α and β are not exactly equal, we opted not to compare α and β.
8 The EMA did not consider the 2 patients in EA for clinical efficacy.

Expanded Access as sole evidence

Strikingly, the evidence from expanded access programs was the only evidence in four cases: (i) sodium phenylacetate and sodium benzoate (FDA), (ii) uridine triacetate (FDA), (iii) cholic acid (FDA/EMA) and (iv) nitisinone (FDA/EMA). We describe these approvals here in more detail.

The combination of sodium phenylacetate and sodium benzoate (i) is indicated for the acute treatment of hyperammonemia in patients with urea cycle disorders, a rare disorder causing dangerously elevated ammonia levels. The observed treatment effect was considerable; historical control data showed a 48% survival rate, whereas 80% of the patients treated under expanded access with sodium phenylacetate and sodium benzoate survived.[21]

Uridine triacetate (ii) treats patients following 5-fluoruoacil or capecitabine overdose. Overdosing can lead to life threatening toxicities, uridine triacetate was therefore administered under emergency expanded access. Historical control data indicated that 16% of patients receiving only supportive care survived. In the expanded access program of uridine triacetate, survival rate was 97%.[22]

Cholic acid (iii) is approved for the life-long treatment of bile acid synthesis disorders. It replaces the abnormal bile acids produced by patients with inborn errors in primary bile acid synthesis. Effectiveness was established by comparing changes in bile acid levels before and after treatment. The submission package only included RWD from expanded access programs, because '*the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, and that it would be contrary to generally accepted principles of medical ethics to collect such information*'.[23]

Nitisinone (iv) is a treatment for hereditary tyrosinemia type 1 (HT-1) and it prevents the flawed conversion of tyrosine. The expanded access program was coordinated from Sweden and patients were treated in 87 different hospitals in 25 countries. Marketing approval was granted '*in view of the rare occurrence and seriousness of the disease, the lack of therapeutic alternatives and the obvious clinical efficacy.*'[24]

DISCUSSION

Having analyzed all available approval documentation, we observe that expanded access programs can provide information on clinical efficacy that impacts regulatory decision making. Furthermore, we find that sponsors and regulators increasingly include RWD from expanded access programs in the efficacy profile of an approval package. The indications of these approvals are characterized by their orphan designation and high unmet medical need, a specific group of conditions. Although the use of RWD may seem a novel application, our study shows that in the case of expanded access, RWD was already used before the year 2000. The expanded access programs propelled by AIDS activism already led to the use of RWD: in 1996, for abacavir (FDA) or 1997 for stavudine (EMA): both compounds are used in the management of HIV.

The specific circumstances in which RWD can complement or even substitute RCTs are in line with the motivations behind the use of RWD from expanded access programs.[25–27] One of these conditions arises when randomization is unethical, for example due to a large unmet medical need.[25] By design, this prerequisite is also a criterion of expanded access: expanded access programs are only for patients in dire need of unapproved treatments. A second situation occurs when further randomized controlled research is infeasible, e.g., when patient populations are small due to low disease incidence.[26] Our study shows that indeed, orphan designations characterize RWD use from expanded access. As the rising interest in personalized medicine results in sample sizes becoming even smaller, data from expanded access may become increasingly important. Although in most cases data collected from expanded access programs complements data from conventional clinical trials, in four approvals in our research expanded access data was the sole source of evidence. The absence of other approved therapies, the rarity of the condition and the large observed treatment effect formed the extraordinary circumstances that led to the approval without evidence from (randomized) clinical trials. In particular conditions it may be challenging to collect data in conventional highly controlled settings and therefore collection of RWD from expanded access programs may be crucial.

Interestingly, there is no guidance on the collection and analysis of data within expanded access programs. This seems rather odd, as our results show that RWD have been used over a period of time, there is an increasing demand of patients and physicians for pre-approval access to investigational treatments and recently, pharmaceutical industry demanded such guidance.[28] Some European countries prohibit the collection of data in an expanded access setting stating that '*no other data except pharmacovigilance data can be gathered which will only be used for the evaluation of the UMN (red: Unmet Medical Need/expanded access) program*'.[29] Well-designed data collection in clinical trials should be considered a prerequisite for scientifically sound

conclusions. expanded access programs harbor inherent flaws – such as data quality issues - and first and foremost: the lack of randomization. Although this should always be kept in mind, it does not mean that the information from patients treated under expanded access should simply be ignored. On the contrary, various approvals rest on data from single-arm clinical trials.[30] Although patients in expanded access programs are not eligible for clinical trials, this does not imply that their treatment data do not qualify for analysis. Data from every patient could provide useful insights and moreover, our study shows that the EMA has considered data from these patients critical in specific approvals. A paradoxical situation arises when individual member states do not allow RWD collection during expanded access programs, yet the EMA uses these RWD in decision making. Harmonization across regulators and individual member states should solve these paradoxes.

We encountered differences in regulatory decisions. In seven cases, the FDA considered data 'pivotal' to the approval whereas the EMA had not approved the product (six cases), or the data were merely considered 'supportive' (one case). Conversely, the FDA has not (yet) approved two products whereas the EMA did. Despite international drug regulation harmonization efforts,[31,32] there is still room for regulatory cooperation across the Atlantic.

Considering our observations in a greater context it appears conventional lines between treatment and research are becoming blurred. This is true for both the field of RWD as a whole and for RWD from expanded access in particular. An example of the former are administrative data used for analyses: data that were not collected for the purpose of research are now found at the heart of an analysis. Similarly for the latter, where expanded access programs were traditionally also meant exclusively for treatment, data collection and thereby research has become a reality. The changing position of expanded access patients from treatment-subjects to (partly) research-subjects, provides a challenge for bioethicists.[11,12,33]

When it comes to comparisons between RCTs and RWD: both have their merits. On the one hand, the control of variability and assurance of data quality in RCTs leads to valid results. On the other hand, these trials target specific homogenous patient populations, e.g., younger and with fewer comorbidities, which limits the generalizability of findings.[26,27] RWD represents a more heterogenous or real-life population, conclusions drawn on RWD are arguably more applicable in day-to-day clinical settings.[10,34] Finding the right balance between RWD and RCTs can become an interesting topic for (bio)-statisticians, (pharmaco)epidemiologists, regulators, and industry.

Awareness of the potential value of RWD from expanded access should facilitate that these data are used appropriately. This helps pharmaceutical industry and regulators determine whether expanded access – and associated RWD – is useful. For patients, this would hopefully result in speedier access to more diverse treatments.

Limitations and future research

Previous literature focused on the legal and ethical implications of expanded access,[4,35–39] or attempted to characterize (US) expanded access programs in terms of associated clinical holds, impact on product labeling, acceptance rates or dates of initiation.[6,40–43] This study is the first to systematically identify, compare, and categorize all EMA and FDA approvals that rely on RWD from expanded access. This differs from previous literature comparing approvals, focusing on the absence of randomized controlled trials.[30] Additionally, to analyze the entire history of RWD use from expanded access, no time limit was used. We are limited by the fact that the Drugs@FDA database includes only drugs and therapeutics (no other biologics) and consistently included reviews only after 1997.

Using recent advances in artificial intelligence to facilitate the processing of documents, we were able to analyze a large number of approvals. As only approvals where expanded access -related appeared were assessed manually, the possibility remains that cases where expanded access data were in fact used were missed because these terms did not appear in the documentation. Although it is unlikely that such terms would not appear in relevant documents, our numbers therefore form a lower bound of the real number of cases where expanded access data were used for approvals.

Future research could focus on statistical implications of combining data from expanded access programs and controlled trials. Additionally, we have only investigated the use of expanded access efficacy data for regulators. Its influence on other stakeholders such as payors or drug developers is a subject that could be pursued through further research.

Conclusion

Expanded access programs can generate real-world evidence prior to drug approval. EMA and FDA increasingly utilize RWD from expanded access in regulatory decision making. The treatments in these approval decisions involved orphan designations and high unmet medical need.

SUPPLEMENTARY MATERIAL

Supplementary Table 1: Overview of FDA and EMA approvals (partly) based on expanded access efficacy data

Generic name	Sponsor	Pivotal[9]	Efficacy[10]	FDA[11]	EMA
abacavir	ViiV Healthcare BV	no	FDA/EMA	1998	1999
afamelanotide	Clinuvel	no	EMA	N	2014
alglucosidase alfa	Genzyme	no	FDA/EMA	2006	2006
amphotericin β	Astellas	FDA	FDA	2000	N
anagrelide	Shire Pharmaceuticals	EMA	FDA/EMA	1997	2004
autologous CD34+ enriched cell fraction	Orchard Therapeutics	no	EMA	N	2016
aztreonam lysine	Gilead Sciences	no	FDA	2010	2009
blinatumomab	Amgen	no	FDA	2014	2015
bosutinib	Pfizer	no	EMA	2012	2013
caspofungin	Accord Healthcare	no	FDA/EMA	2001	2001
cholic acid	Retrophin	FDA/EMA	FDA/EMA	2015	2015
clarithromycin	Abbott Pharmaceuticals	FDA	FDA	1993	N
clofarabine	Genzyme	no	FDA	2004	2006
daclatasvir dihydrochloride	Bristol-Myers Squibb	no	FDA	2015	2014
defibrotide	Gentium	no	FDA	2016	2013
dinutuximab β	EUSA Pharma	EMA	EMA	N	2017
fish oil triglycerides	Fresenius Kabi	FDA	FDA	2018	N
glucarpidase	BTG	FDA	FDA	2012	W
idebenone	Santhera Pharmaceuticals	no	EMA	N	2015
imatinib	Novartis	no	FDA/EMA	2001	2001
isavuconazole	Basilea Pharmaceutica	no	EMA	2015	2015
ivermectin	Merck Sharp Dohme	no	FDA	1996	N
lamivudine	GlaxoSmithKline	no	EMA	1998	1999
linezolid	Pharmacia & Upjohn	no	FDA	2000	N
lutetium (177Lu) oxodotreotide	Advanced Accelerator Applications	FDA/EMA	FDA/EMA	2017	2017
mercaptamine hydrochloride	Recordati Rare Diseases	no	EMA	2012	2017
miltefosine	Knight Therapeutics	no	FDA	2014	N
nitisinone	Swedish Orphan Biovitrum	FDA/EMA	FDA/EMA	2002	2005
pitolisant	Bioprojet Pharma	no	EMA	N	2016
propranolol hydrochloride	Pierre Fabre Dermatologie	no	FDA/EMA	2014	2014

9 Pivotal depicts if FDA/EMA used data from EA in a pivotal way to support the efficacy profile.
10 Determines whether FDA and or EMA used data from EA to support the efficacy profile.
11 Year of EMA/FDA approval (if applicable). W: Withdrawn, N: Not approved.

Generic name	Sponsor	Pivotal[9]	Efficacy[10]	FDA[11]	EMA
sodium phenylacetate and sodium benzoate	Medicis Pharmaceutical	FDA	FDA	2005	N
stavudine	Bristol-Myers Squibb	no	EMA	1994	1996
stiripentol	Biocodex	no	FDA/EMA	2018	2007
trabectedin	Pharma Mar	no	EMA	2015	2007
trientine tetrahydrochloride	GMP-Orphan SA	no	EMA	N	2017
uridine triacetate	Wellstat Therapeutics	FDA	FDA	2015	N
velmanase α	Chiesi Farmaceutici	EMA	EMA	N	2018
vestronidase α	Ultragenyx	FDA	FDA	2017	2018
ziconotide	RIEMSER Pharma	no	EMA	2004	2005

CHAPTER 6

Real-world data from expanded access programs in health technology assessments: a review of NICE technology appraisals

Polak TB, Cucchi DGJ, van Rosmalen J, Uyl-de Groot CA.
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ABSTRACT

Objectives To quantify and characterize the usage of expanded access data in National Institute for Health and Care Excellence (NICE) technology appraisals (TAs). Expanded access offers patients that are ineligible for clinical trials or registered treatment options access to investigational therapies. Although expanded access programs are increasingly used to collect real-world data (RWD), it is unknown if and how these data are used in NICE health technology assessments.

Design Cross-sectional study of NICE appraisals (2010-2020). We automatically downloaded and screened all available appraisal documentation on NICE website (over 8,500 documents), searching for EA-related terms. Two reviewers independently labelled the expanded access usage by disease area, and whether it was used to inform safety, efficacy, and/or resource use. We qualitatively describe the five appraisals with the most occurrences of EA-related terms.

Primary outcome measure Number of technology appraisals that used expanded access data to inform safety, efficacy and/or resource use analyses.

Results In 54.2% (206/380 appraisals) at least one reference to expanded access was made. 21.1% (80/380) of the TAs used expanded access data to inform safety (n=43), efficacy (n=47) and/or resource use (n=52). The number of TAs that utilize expanded access data remained stable over time, and the extent of expanded access data utilization varied by disease area (p=0.001).

Conclusion NICE uses expanded access data in over one in five appraisals. In synthesis with evidence from well-controlled trials, data collected from expanded access programs may meaningfully inform cost-effectiveness modelling.

INTRODUCTION

Novel drug therapies are important drivers of increased health care spending. In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) conducts technology appraisals (TAs) to evaluate cost-effectiveness of technologies (e.g., drugs, medical devices) and to determine their impact on health care budgets.[44] These evaluations are conducted using a variety of data sources, such as randomized controlled trials (RCTs) or observational studies.[45,46] In this research, we explore the use of data in NICE TAs from another source: expanded access programs.

A positive appraisal determination from NICE forms the main pathway for novel pharmaceutical technologies to access the National Health Service (NHS) and become available for patients across the UK. The health technology assessment (HTA) usually starts with the submission of evidence on clinical effectiveness and costs by the pharmaceutical company. The submission is scrutinized by an independent Evidence Review Group (ERG), which critically reviews the manufacturer's submission and performs additional exploratory analyses of cost-effectiveness; in some cases, the ERG even re-analyses clinical data.[44,47,48]

Patients, patient advocacy groups, and physicians working within the NHS also contribute to NICE's appraisals. The resulting qualitative input is considered in the formal analyses conducted by the manufacturer and the ERG. The entire evidence is assessed by NICE's Appraisal Committee and forms the basis of their appraisal determination.[49] More detailed information on NICE's processes can be found on their guidance website (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance).

HTA bodies are particularly keen to know how technologies will use resources, yield benefit, and attribute risks in the real-world patient population for which treatment will potentially be reimbursed.[10] Real-World Data (RWD) are 'information on health care that is derived from multiple sources outside typical clinical research settings', such as electronic health records, claims and billing databases, or patient registries.[34] RWD is typically generated after a drug comes to market (post-approval). At the time of the reimbursement decision however, most of the available data stems from clinical trials (pre-approval). Noteworthy, payers may use (real-world) data from patients that have been treated outside of clinical trial settings, but prior to marketing authorization.[44–46] These patients can receive treatment via expanded access programs.

Expanded access (EA) is a pathway to access investigational medicine for patients who suffer from life-threatening conditions, who cannot enter clinical trials, and have exhausted all approved treatment options. It is also known as 'compassionate use', 'early access' or 'non-trial pre-approval

access'.[2] The primary intent of expanded access programs is to provide patients and physicians in dire need with potential treatment options outside of clinical trials. Secondary, such programs may potentially collect real world data in a regulatory pre-approval setting, but the generation and useability of evidence derived from these programs remains a topic of debate.[11,12,50–54]

Data from expanded access programs may be used for various purposes in the appraisal process, for example to inform formal safety or efficacy analyses, to inform resource use and associated costs in real-world settings, to estimate the size of the patient population, or to gain insights into the treatment experience from patients or physicians that participated in an expanded access program. These data are increasingly accepted to support evidence of clinical efficacy by regulators, especially when collecting data in controlled settings is infeasible, such as in (ultra-) rare diseases, or is deemed unethical, in the case of extremely large treatment effects.[50] However, the use of expanded access data by payers or HTA bodies remains unquantified. Understanding the role of expanded access data in TAs may clarify the value of these data for payers, pharmaceutical industry, physicians and patients, and is relevant for cost-effectiveness decision making and evaluation of HTA policy. Therefore, we here investigate the usage of expanded access data in NICE decision making by reviewing all appraisals presented to NICE between 2010 and 2020.

METHODS

Documents relating to all TAs conducted are provided on the NICE website. We investigated TAs published between January 1st 2010 and January 1st 2021. Terminated, withdrawn, or replaced appraisals were removed as documentation was unavailable. A schematic overview of our workflow is provided in Figure 5.

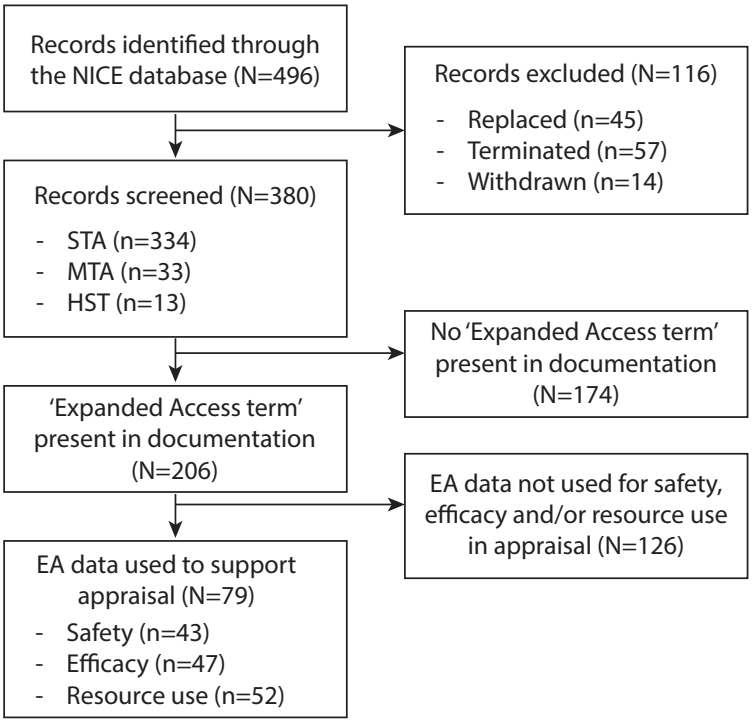


Figure 5: Screening and selection of technology appraisals from NICE.

STA, single technology appraisal. MTA, multiple technology appraisals. HST, highly specialized technology. EA, expanded access. NICE, National Institute for Health and Care Excellence

We wrote a computer script (i.e., a web scraper)[50] to automatically list and download all documentation (e.g., manufacturer submissions, ERG report, final appraisal determination) available through NICE's website. Subsequently, the script extracted the text from these documents and automatically screened whether the text contained 'expanded access (EA) terms', like 'Compassionate Use', 'Expanded Access' 'Early Access', etcetera, as well as all possible spellings thereof. A detailed protocol, including all search terms, is available in the Supplementary Material. The data and code from the paper are available on the GitHub from the first author, https://github.com/TobiasPolak. When at least one of these 'expanded access terms' was present, two authors (T.B.P. and D.G.J.C.) independently and manually, reviewed the context of the term.

We primarily labelled the data usage with one or more of the following categories:

1. Safety: expanded access data were used to evaluate the safety profile
2. Efficacy: expanded access data were used to evaluate the efficacy profile

3. Resource use: expanded access data were used to inform cost parameters
4. Trivial: expanded access data were not used or trivially mentioned in the appraisal

Patients and physicians also share their treatment experience. As the impact of these accounts is harder to quantify, we did not include them in our main analysis but secondarily labelled:

1. Treatment experience: When patients or physicians cited experience within the expanded access program.

Discordance was resolved by discussion between the two reviewers. To give the reader a sense of these different types of usage, examples are provided in the Results section. Additionally, we provide a narrative summary of the five appraisals that contain the most occurrences of the search terms to illustrate the use of expanded access data qualitatively. Lastly, TAs were classified as single technology appraisal (STA), multiple technology appraisal (MTA), or highly specialized technology (HST). All TAs were categorized according to their area of disease.

Statistics

The Spearman rank correlation test was used to detect time trends in the yearly number of appraisals using expanded access data. We performed a Pearson chi-square test to assess whether the proportion of appraisals that included expanded access data differed by disease area. For all significance testing, we set the 2-sided significance level at 0.05.

RESULTS

We screened all 496 TAs conducted between January 1st, 2010 and January 1st, 2021. This ranged from Technology Appraisal 185 (TA185) to TA667 and from Highly Specialized Technology 1 (HST1) to HST13. N=116 appraisals were excluded (for details, see Figure 5). The remaining 380 appraisals had 8,925 documents that were downloaded and screened.

In 54.2% (206 of 380 appraisals) at least one reference to expanded access was made. In total, 80 out of 380 (21.1%) of the TAs used expanded access data to inform safety (n=43), efficacy (n=47) or resource use (n=52). As a single TA could have multiple labels, there is overlap between safety, efficacy and resource use. This is depicted in Figure 6A. Additionally, in 54 appraisals (14.5%) the expanded access program was cited by patients or physicians as treatment experience.

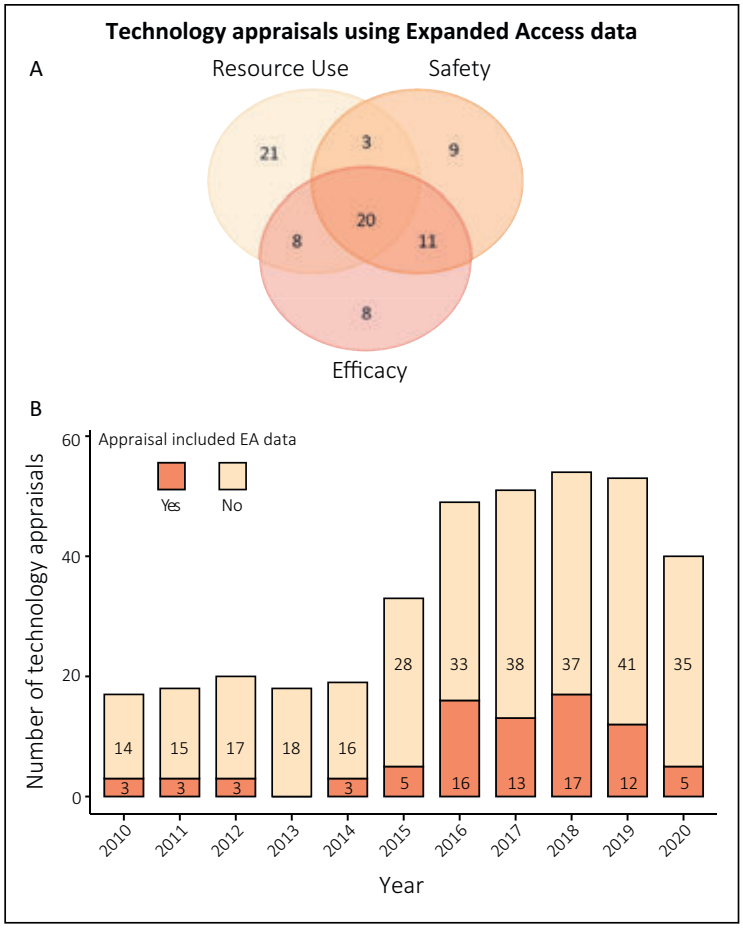


Figure 6: Technology appraisals using expanded access (EA) data to support safety, efficacy and/or resource use. A: Venn-diagram displaying the overlap of safety, efficacy, and/or resource use labelling of technology appraisals. B: Bar chart of technology appraisals published between January 1st 2010, and January 1st 2021 that did ('Yes') or did not ('No') include data expanded access programs to support safety, efficacy and/or resource use.

Although there is a significant increase over time in the absolute use of expanded access data by payers ($\rho = 0.73$ and $p = 0.011$; Figure 6B), there is no evidence of a significant increase in use of expanded access data over time relative to the total number of appraisals conducted ($\rho = 0.32$ and $p = 0.332$).

Significant differences ($\chi^2 = 38.8$, $p = 0.001$) exist in the disease areas that did versus those that did not include expanded access data. Oncology and hematology together account for 66% of the appraisals with expanded access data, whereas they make up 50% of the entire fraction of

appraisals. On the other hand, disease areas such as cardiology, gastroenterology, endocrinology, dermatology, rheumatology, and ophthalmology jointly make up 24.5% of all appraisals, whereas they merely account for 2.6% of the appraisals that included expanded access data. These results can be found in Table 2.

Table 2: Technology appraisals that did ('Yes') or did not ('No') include expanded access data to support the profile of safety, efficacy and/or resource use, classified on disease area.

	Included expanded access data			
Disease area	**No**[1]	**Yes**[1]	**Total**[1]	p-value[2] 0.001
Benign hematology	5 (1.7%)	3 (3.8%)	8 (2.1%)	
Cardiology	14 (4.7%)	0 (0%)	14 (3.7%)	
Dermatology	12 (4.0%)	1 (1.3%)	13 (3.4%)	
Endocrinology	12 (4.0%)	0 (0%)	12 (3.2%)	
Gastroenterology	13 (4.3%)	0 (0%)	13 (3.4%)	
Hematology	35 (12%)	20 (25%)	55 (14%)	
Internal medicine	23 (7.6%)	9 (11%)	32 (8.4%)	
Neurology	14 (4.7%)	6 (7.6%)	20 (5.3%)	
Oncology	106 (35%)	32 (41%)	138 (36%)	
Ophthalmology	18 (6.0%)	0 (0%)	18 (4.7%)	
Psychiatry	3 (1.0%)	1 (1.3%)	4 (1.1%)	
Pulmonology	6 (2.0%)	4 (5.1%)	10 (2.6%)	
Rheumatology	22 (7.3%)	1 (1.3%)	23 (6.1%)	
Surgery	4 (1.3%)	1 (1.3%)	5 (1.3%)	
Urology	1 (0.3%)	1 (1.3%)	2 (0.5%)	
Vascular medicine	13 (4.3%)	0 (0%)	13 (3.4%)	
Total	301 (79%)	79 (21%)	380 (100%)	

[1] n (%) [2] Pearson chi-square test

Examples

To give the reader a better sense of the main labels 'safety, efficacy, resource use' as well as the secondary 'treatment experience' label, we here provide illustrative examples from the TAs that were supported by expanded access data.

Safety

Safety data from expanded access programs are often described rather qualitatively, supporting results from clinical trials. For example, in the appraisal of gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, the appraisal committee noted:

> *'The favorable safety profile of gefitinib demonstrated in the phase III studies is consistent with that observed in everyday settings. In addition to the data from clinical trials, the Early Access Program for gefitinib in Caucasian patients indicated that gefitinib is well tolerated by*

> *patients with advanced or metastatic NSCLC. The majority of ADRs associated with gefitinib are mild in nature and those most commonly reported are grade 1/2 diarrhoea and skin reactions.'*
>
> Manufacturer submission, Safety and tolerability, TA192

Alternatively, safety signals from expanded access programs can be quantitatively incorporated in cost-effectiveness analyses. When evaluating ocrelizumab for treating relapsing–remitting multiple sclerosis, the committee noted that an important safety signal from the compassionate use program is lacking from the current analysis:

> *'The committee heard that there has been the 1 case of PML (progressive multifocal leukoencephalopathy, red.) following treatment with ocrelizumab in the compassionate-use programme in Germany, (...). It concluded that the economic model should have included a risk of PML for ocrelizumab.'*
>
> Appraisal consultation, Adverse events in the economic model, TA533

Efficacy

Efficacy data from expanded access programs can also be used, together with data from clinical trials, to estimate overall efficacy of the technology appraised. In the evaluation of lutetium (177Lu) oxodotreotide for treating irresectable or metastatic neuroendocrine tumors, response rates were obtained from the 'Erasmus study'. The Erasmus study was a compassionate use program conducted at the Erasmus MC. The data from this program are summarized as:

> *'In a single centre non-controlled phase I/II open-label study (The Erasmus study, red.), conducted in 810 Dutch patients with different somatostatin receptor positive tumour types, the objective response rate (ORR) for the full analysis set (FAS) population with GEP-NETs and bronchial NETs (360 patients) was 44% (95% confidence interval [CI] 38% - 49%).'*
>
> Manufacturer submission, Executive summary, TA539

NICE requires that benefits of technologies are evaluated using quality-adjusted life years (QALYs), as NICE's decision to recommend or not recommend a product for reimbursement depends (among other things) on the willingness-to-pay for an incremental year in perfect health – the so-called cost-per-QALY approach. In the evaluation of cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel, the expanded access program was used to gather quality of life data not collected during the routine clinical development:

'The company did not collect data on health-related quality of life in TROPIC (the RCT, red.), so it took utility values from the UK Early Access Programme (EAP) for cabazitaxel. The programme measured the health-related quality of life (using the EQ-5D) of men who had been treated with cabazitaxel after docetaxel.(…)'

'(…) One hundred and twelve patients participated in the UK EAP at 12 UK Cancer Centres. All had mCRPC with disease progression during or after docetaxel and were similar in baseline patient characteristics to the population in TROPIC. (…) Safety assessments were performed prior to each cycle and HRQL recorded at alternate cycles using the EQ-5D-3L questionnaire and visual analogue scale (VAS).'

Committee papers, Health-related quality of life, TA391

Resource use

Expanded access data can also be used to inform other parameters in cost-effectiveness modelling. Such models are often based on Markov chains, which describe the state of the disease that patients are in at a given time point. These models require cost per state and transition probabilities or rates between states. Registries, or other real-world data sources, are frequently used to estimate such data. In the appraisal of sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C, transition probabilities from decompensated liver cirrhosis to death are modelled via a Beta-distribution and the input parameters are provided from the expanded access program:

'Variable: From decompensated cirrhosis to death
Distribution and parameters: Beta; α*=46.5;* β*=147.2*
Source: EAP data (expanded access program, red.)'
Manufacturer submission, Sensitivity analyses, TA507

A different, direct resource use example is given in the evaluation of ipilimumab for previously treated irresectable malignant melanoma. The dosing of ipilimumab is weight dependent. Hence, to estimate the number of vials needed for treatment of UK patients, an estimate of the (UK) patient population weight is required. This weight is calculated via:

'Patient level analysis of the weight of UK clinical trial patients in MDX010-20 (n=55), and the weight of UK patients in the ipilimumab compassionate use program (n=258), from these weights, the mean number of vials required (assuming no vial sharing) is calculated.'

'Results from these analyses showed that the dose of ipilimumab given per patient per induction has a large impact on the ICER with the minimum dose given in the trial and compassionate use programme (3 x 50 mg) resulting in an ICER of £38,387 per QALY gained

and the maximum dose (2 x 200 mg) given resulting in an ICER of £88,788 per QALY gained.'

Manufacturer submission, Intervention and comparators costs, TA268

Treatment experience

NHS professionals share their opinions and experience on the technology appraised in expert committee meetings. In the appraisal of patisiran for treating hereditary transthyretin amyloidosis, the Head of the National Amyloidosis Centre (NAC) is asked 'how data on real-world experience in this condition compare with clinical trial data?'. His response is:

'The experience of my colleagues at the NAC treating patients through compassionate access (over one year) and Early Access to Medicine Schemes has been extremely favourable. Remarkable clinically significant improvements of well-being and function have occurred in a majority of cases, including regaining the ability to walk unaided.'

Clinical expert statement, HST10

Patients, caregivers, or patient group representatives are also provided the opportunity to share their experience with the appraised treatment. The assessment of nusinersen for treating muscular atrophy sparked comments from parents with children that suffer from this disease:

'My son is currently receiving Spinraza at Gosh for type 1c SMA. He was lucky enough to be included into the expanded access program for a select group of children. Since receiving his treatment we have watched the transformation of a seriously weakening child to a thriving boy who has gained significant progress in his motor function and health, we are continually amazed by his progress. He starts preschool in the coming weeks, an achievement we never thought possible. (...)'

Patient/caregiver stakeholder comment, TA588

The above provides qualitative examples of EA usage in NICE appraisals. To further illustrate how expanded access data are appraised by the manufacturer, ERG and NICE committee, and what the advantages and limitations of its use may be, a detailed discussion of the top five appraisals in which the search terms most frequently occurred can be found in the Supplementary Material. This includes representative examples in the areas of hemato-oncology (e.g., prostate cancer, follicular lymphoma) and rare diseases (e.g., spinal muscular atrophy).

DISCUSSION

In this review, we combined automated documentation searches with double, independent manual review to screen NICE documentation on the usage of expanded access data for HTA. We have found that data from expanded access programs are frequently included: 21.1% of the TAs used expanded access data to evaluate safety, efficacy/effectiveness, or resource use of the appraised technology. The use of data from expanded access programs appears to remain stable over the years. Additionally, patients and physicians share their treatment experience from an expanded access program in 14.2% of the appraisals.

The disease areas of the appraisals that included expanded access data differed significantly from the overall distribution of disease areas from all appraisals investigated between 2010 and 2021. Oncology and hematology account for the lion's share (66%) of expanded access data usage, yet account for half (50%) of all TAs conducted. Although 'the life-threatening or seriously debilitating' prerequisite for expanded access is often present in hemato-oncologic malignancies, cardiac or ophthalmologic illnesses can also be severely limiting.[55,56] Cardiology and ophthalmology account for 8.4% of all TAs, but none (0%) of these programs used expanded access data (or even mentioned it). There is a range of possible explanations for this discrepancy. Perhaps, drug developers in these areas may be less familiar with collecting and using expanded access data, or cardiologists and ophthalmologists may be less acquainted with expanded access than haemato-oncologists – simply because expanded access may be less warranted in these disease areas.[57,58]

Compared with regulatory submissions to the EMA and the FDA, submissions to NICE more frequently include expanded access data. The EMA and FDA used expanded access data to support efficacy in 49 regulatory approvals over 25 years (± 2 annually).[50] In this work, we find that NICE used expanded access to inform cost-effectiveness in 76 over 11 years (± 7 annually). One reason for this may be that payers have a higher uptake of RWD in their decision making. Furthermore, they also assess comparative effectiveness rather than efficacy. Modelling cost and comparative effectiveness by definition necessitates a variety of input parameters, every one of them potentially coming from different sources, such as expanded access.

Whether using expanded access data (or other non-randomized data) for payer decision making is wise, depends in part on the robust design and execution of the expanded access program, and the relevance to the decision problem.[59] The instances in which the FDA and the EMA assessed efficacy mainly based on expanded access data, are scarce, and characterized by (i) a high unmet medical need (ii) a rare disease population and (iii) large treatment effects.[50] Additionally, we witnessed twice (TA391, TA491) that health-related quality-of-life (HRQoL) data were not

gathered during the conventional clinical trials but were captured in the expanded access program. Although data from expanded access programs can bridge an evidence gap, HRQoL data should simply have been collected during all stages of clinical development. For safety, the use of registries, post-approval safety studies, or pharmacovigilance during expanded access, is useful to detect infrequently occurring adverse events. Indeed, we identified such an example in TA533, where the compassionate use program led to the identification of a rare but serious adverse event. Overall, the evidence for assessing safety and efficacy should primarily come from regulatory studies and can be synthesized with RWD or other non-randomized sources, such as expanded access programs.

Including expanded access can have several advantages, as it can increase sample size, add robustness, inform additional parameters - such as HRQoL - or aid to estimate effects for patients that were excluded from the trial, but were included in the expanded access program. Such patients are generally older and frailer,[10,60,61] and thus collecting data in these populations helps to extrapolate results on safety and efficacy found in RCTs. Estimates of resource use parameters that are derived from clinical trials, such as adherence, monitoring, or the number of hospital visits, can even be more distinct from real-world settings. Therefore, expanded access data can play a useful role in informing resource use parameters. Furthermore, modelling resource use requires estimates of a large number of input parameters, such as costs, incidence and also transition parameters that determine the amount of time spent in a disease state. Some of these parameters can only be estimated from studies with lengthy follow-up periods, so that patient or population registries or expanded access programs would be best suited to inform decision making on these model inputs. Finally, trial values may not be sufficiently informative, as they are typically multinational and do not contain data relevant to a particular national health system.

The regulatory status of data collection during expanded access programs is a matter of debate.[11,12,14,16,50,51] In Europe, individual Member States regulate expanded access programs.[5] Different countries may issue conflicting statements that can be at cross with EMA decision making.[50] This also resonates in appraisals. For example, we read in the appraisal of cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma:

> *'While formal data collection is not permitted from a regulatory standpoint, the safety of cemiplimab at the flat 350mg dose in a real-world setting will be monitored.'*
>
> Manufacturer submission, Safety overview, TA592

This begs the questions of who decides what formal and informal data collection is and whether all examples put forth in this paper where impermissible for regulators. Regardless of regulatory requirements, it can be a source of frustration when expanded access data are not available, as one Advisory Group (AG) noted:

> *'The lack of any efficacy data from the compassionate use program is particularly disappointing,'*
>
> AG response to company comments, AG conclusions, TA535

Although the primary intent of expanded access programs is treatment provision and not to conduct research, it seems awkward to treat patients with investigational medicine and not to collect data to inform safety and efficacy. Furthermore, it is difficult to precisely determine where treatment-intent ends and research-intent starts. The changing nature of expanded access programs from sole treatment-intent to treatment-intent with data collection is a current topic of debate among bioethicists.[11,33,52] We stress that data collection during expanded access should be light-weight and must not disproportionally burden patient and physicians – hence, a smart design should facilitate data to be collected.[52] If so, expanded access programs can be the first source of RWD to inform HTA evaluations gathered in a pre-approval setting – this makes expanded access data different from general RWD sources (e.g., electronic health records or claims and billing data), as the latter will typically only start generating evidence once the drug has been approved. Results from expanded access programs can be obtained via peer-reviewed publications, if published. Alternatively, data can be requested via the medical company using data sharing platforms, such as Vivli.[62] Finally, data may be available through local investigators (see HST7, Supplementary Material).

Limitations and future research

Our work has several limitations. First, we only reviewed TAs from one HTA body: NICE. Formally, NICE's decisions are only valid within their UK jurisdiction, but informally they lead the way for other European HTA bodies - either via setting an example or via reference pricing. We have chosen NICE for our review as they have the longest history of HTA assessment and ample documentation publicly available. For other HTA bodies, results may be different. Future research should confirm whether our results uphold for other HTA bodies. Preliminary findings presented at a conference concluded that using expanded access data gathered within French compassionate use programs had a positive impact on reimbursement discussions.[63] Second, we may have missed use-cases of expanded access data in payer submission as companies or reviewers may have used other terms to indicate expanded access programs (or failed to have done so). Our automated algorithm facilitates high throughput of document screening in health policy analysis, but it may have missed cases that would have been identified in manual evaluation. Therefore, our estimates should be

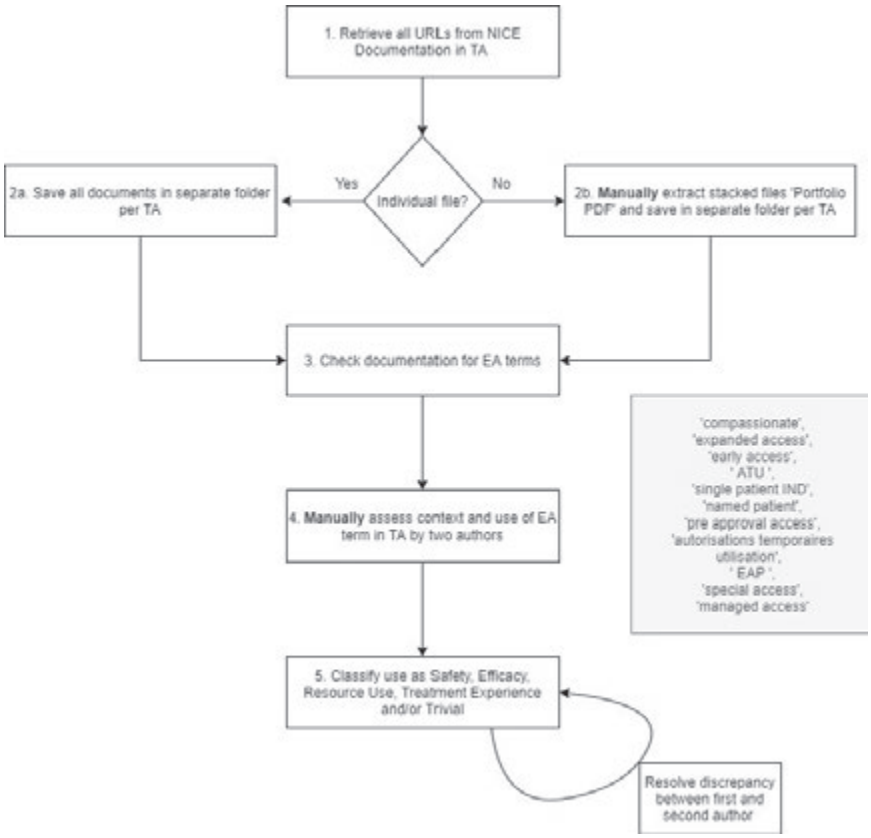
interpreted as a lower bound of expanded access use in NICE appraisals. Lastly, we were unable to exactly quantify the added value of expanded access data. As we lack a counterfactual, we do not know what would have happened without the inclusion of expanded access data. Additionally, it is difficult to measure the impact of expanded access data, as it is not always clear how these data have exactly been used: the use of expanded access data – and the appraisal thereof – in HTA by the manufacturer, ERG or NICE committee are difficult to quantify due the complexity and extent of the discussions described in the documentation. Although we have provided the reader with both high-level quantitative statistics and with illustrative qualitative examples from our data set, future research could attempt to systematically analyze these topics.

Conclusion

Expanded access data are used in over one in five (21.1%) NICE appraisals, and this number appears to remain stable over time. In general, adding data from expanded access can yield more real-world information. Especially to estimate the resource use, pre-approval expanded access data can play a vital role informing post-approval real-world usage. In synthesis with evidence from well-controlled regulatory studies, data collected from expanded access programs may meaningfully inform NICE decision making. Further research is required to understand when expanded access data can and should be included in health technology assessments.

SUPPLEMENTARY MATERIAL

A. Protocol Workflow



Supplementary Figure 1: Protocol workflow

B. Top Five Most Referenced Appraisals

TA391 Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel

In 2016, NICE assessed the cost-effectiveness of anticancer taxane therapy cabazitaxel for the treatment of metastatic prostate cancer that relapsed after it was treated with docetaxel. Sanofi was the submitting company and the School of Health and Related Research (ScHARR) produced the evidence review group (ERG) report. TA391 is an updated appraisal of TA255.

In this appraisal, the company did not collect data on health-related quality of life in the main trial that investigated the use of cabazitaxel, so it took utility values from the expanded access programme in the United Kingdom. The ERG found several issues with data from this program: the open-label nature, generalizability (patients were potentially more fit than in the trial), the analysis was performed at interim and had not yet been subject to peer review.

The Committee partly shared the vision of the ERG: '*the Committee was concerned about the uncertainty around the utility value and whether the utility value as calculated from the early access programme could be applicable to the wider population with hormone-refractory metastatic prostate cancer refractory to docetaxel treatment*'. On the other hand, the committee also appreciated the efforts of the company: '*The committee acknowledged the limitations of using data from the UK early access programme but, in the absence of more robust evidence on health-related quality of life, it concluded that the company had used the best available data to estimate utility values.*'

The initial Final Appraisal Determination did not recommend the use of cabazitaxel, leading the company to appeal to the Appeal Panel, focusing in part on the interpretation of the EAP trial. ('*the context of the EAP trial was misinterpreted, data from the EAP trial were incorrectly interpreted, and the nature of interim data was misunderstood by the committee*'). The Appeal Panel '*understood both sides' positions and regarded them both as reasonable*' and as such dismissed all the grounds of appeal. After a new confidential discount to the price of cabazitaxel was arranged, its use has been recommended within the NHS.

TA667 Caplacizumab with plasma exchange and immunosuppression for treating acute acquired thrombotic thrombocytopenic purpura

In 2020, NICE assessed the cost-effectiveness of the humanized antibody caplacizumab, used together with plasma exchange and immunosuppression for the treatment of acute acquired thrombotic thrombocytopenic (TTP) purpura. Caplacizumab inhibits the interaction between Von-Willebrand-factor and thrombocytes, thereby reducing the aggregation of thrombocytes which is typical for TTP. Sanofi was the submitting Company and the Peninsula Technology Assessment Group (PenTAG) produced the evidence review group (ERG) report.

In the main trial for caplacizumab (HERCULES, N=145), no patient died while on treatment with caplacizumab (0%). Due to the unreliability of mortality data from the trial (clinicians noted that mortality was unlikely to be 0%), data from the compassionate use programme was brought in. At the first data lock, eight out of 187 (4.2%) of the patients perished, and 9/239 (3.8%) at second data lock.

The limited information available rendered the interpretation of these data difficult. Mortality from the compassionate use programme was based on deaths reported via Adverse Event Reporting. No baseline characteristics were available to compare patients among data sources: *The monitoring programme for caplacizumab was a compassionate use programme rather than a data collection programme. As such, the only information available includes where the patient was from, whether caplacizumab was received and whether the patient died, (…). Therefore, an assessment of the similarity between mortality sources using patient characteristics could not be conducted*.

> *Therefore, the ERG 'notes potential ambiguities and sources of bias in the compassionate use program (…) including unknown follow-up periods, unclear recruitment process, and that it draws from an international population.'*

The company interjected that '*the compassionate use programme estimates selected to represent caplacizumab in the comparison are, if anything, too high*' – as *'clinicians agreed that treatment with caplacizumab is started later in the compassionate use programme that it would be if it was made available through routine funding (as requests are individual and caplacizumab is not available on site). Mortality data based on this programme should therefore be considered as the maximum mortality expected with caplacizumab.'*

The committee agreed that it was impossible to '*estimate reliably the extent of the benefit using the randomised trial data*' and recognized the need for use of data on deaths from the global compassionate use scheme. It noted that the absolute rate of death for people treated with caplacizumab under the compassionate use scheme was likely to be valid, but that the relative benefit ascribed to caplacizumab from observational data '*was very likely to be confounded*'.

Furthermore, the committee noted that *'Some potential cost savings associated with caplacizumab may not be included in the company's model'* as '*The company stated that, based on its observations from the compassionate use scheme for caplacizumab, in NHS clinical practice, people would have it for a shorter duration than in the trials. The committee in general prefers not to disassociate estimates of cost and effectiveness from a trial. However, it appreciated that many assumptions about caplacizumab's effectiveness in this model were not taken from the main trial. It also thought that some potential cost savings associated with caplacizumab may not have been included in the company's model.*'

Despite the remaining uncertainty, *'(...) the assumptions in the economic modelling are plausible. Also, there are potential benefits with caplacizumab that are not included in the cost-effectiveness estimates. Overall, the estimates are within the range normally considered a costeffective use of NHS resources. So, caplacizumab is recommended for treating acute acquired TTP.*'

TA588 Nusinersen for treating spinal muscular atrophy

In 2018-2019, NICE assessed the cost-effectiveness of the antisense oligonucleotide nusinersen, used in the treatment of spinal muscular atrophy. Nusinersen promotes the formation of the functional SMN protein, through modulation of intron splicing, essential for normal function of motor neurons. Sanofi was the submitting Company and the Peninsula Technology Assessment Group (PenTAG) produced the evidence review group (ERG) report.

NICE initially did not recommend the use of nusinersen for treating SMA as it was not deemed a cost-effective use of NHS resources. NICE consulted with the public and professionals and noted that '*Following consultation, the committee heard that there was real-world evidence that would be relevant for the committee's decision making that had not been considered by the company.*'

Although the Company briefly touches upon data from the early access programme (EAP) in UK and Ireland (63 patients, of which 25 males and 38 females) and additionally points at the publication of a second European EAP conducted in other European countries (N=36, Gargaun et al.), the Spinal Muscular Atrophy Support UK and The SMA Trust points to several other studies in the consultation period: '*We note that the real-world studies only review outcomes for children with SMA Type 1 for the first six months of treatment but consider 'real world' evidence critical to decision making. They all assist with confirming the certainty of evidence of effectiveness (see below). In particular we refer to: Reviews of the Expanded Access Programme:*

- *Europe - 33 children aged from 8.3 to 113.1 months - December 2016 - May 2017. Aragon-Gawinska, K et al. (2018)*
- *Australia – 16 patients aged 2.5 months to 35.7 years November 2016 – September 2017 Farrar, M et al. (2018)*

- *England - Great Ormond Street Hospital – 21 patients aged 8.3 – 113.1 months March – October 2017 Tillmann, A et al. (2018)*
- *Germany – 61 patients aged 1 – 93 months in seven neuromuscular centres November 2016 – June 2017 Pechmann, A et al. (2018)*
- *Italy – 104 patients – aged 3 months – 19 years 9 months - first six months of EAP Pane, Pane M et al. (2018)*
- *Hoy, S (2018)*'

The committee responded: '*The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.*

The company stated that they did not consider these data '*because the results were consistent with the clinical data that it had presented and, in comparison, the data were immature, would be from non-UK sources and would only include SMA type 1'.* The committee stated '*that it would have liked the company to identify supportive real world evidence, given the clinical uncertainties identified.'* - but also acknowledged that the company already included several types of data.

In the end, Nusinersen became available through a managed access agreement*', including the collection of more data to address the uncertainties.*'

HST7 Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency

In 2018, NICE assessed the cost-effectiveness of strimvelis, used to treat severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID). Patients with ADA-SCID have a dysfunctional gene, needed for the production of the enzyme adenosine deaminase (ADA), leading to defective lymphocytes and thereby severe immunodeficiency. Strimvelis consists of genetically modified bone marrow cells of the patient, reactivating ADA production. Strimvelis is used in patients who are ineligible for allogeneic bone-marrow transplantation. Since strimvelis is a gene therapy product, its cost-effectiveness is evaluated through a 'highly specialised technology guidance' (HST). GlaxoSmithKline was the submitting company, and the Centre for Reviews and Dissemination and Centre for Health Economics in York prepared the Evidence Review Group (ERG) report.

The submission of data for the gene therapy Strimvelis comprised a mix of evidence sources: '*The safety and efficacy of Strimvelis have been evaluated in a programme comprising 2 pilot studies, 1 pivotal study, a compassionate use programme (CUP), and a long-term follow-up (LTFU) study.*'

The company preferred to report the results of the clinical trials together, as an '*integrated population', with results from the Named Patient Programme (NPP) presented alongside as supportive evidence. The company stated that it did not include the NPP data in the integrated population because the population of the NPP was substantially different to the population in the other trials, and that it could not access all the patient-level data because the NPP was a clinician-initiated process.*

The ERG critiqued this decision: '*However, the ERG did not consider it appropriate that data from the Named Patient Population were excluded from the narrative synthesis of clinical effectiveness evidence. This is particularly important given the small sample size of the Strimvelis Integrated Population (n=18) and therefore the need to consider all available data when evaluating the effectiveness of this treatment.*'

Indeed, the Company even requested (to no avail) the ERG to remove the wording 'NPP study', as '*Noting the NPP as a study wrongly indicates that the NPP is part of the Strimvelis clinical programme and therefore at the same level in terms of availability and quality of evidence.*

NICE however specifically requested more information on these patients. '*A3. Please provide a narrative summary of the data (e.g., in terms of overall survival, intervention-free survival, adverse events etc.) available from the named patient programme using the same format as in the main clinical effectiveness section on the Strimvelis Integrated Population.*'

As the named-patient program was investigator-initiated, access to data was limited: 'A3. *Table 1 contains the requested information, as available, for patients in the NPP. Data on the proportion of patients with viral infection at baseline are not available. As the ERG has noted, the NPP is not run by GSK, which limits access to data and as such it is difficult to speculate on wider applicability of these immature and incomplete data. The programme is ongoing and data are not scheduled for formal analysis until all patients have reached 3 years of follow-up.*'

Strimvelis is recommended as a treatment option for treating adenosine deaminase deficiency–severe combined immunodeficiency (ADA–SCID) when no suitable human leukocyte antigen-matched related stem cell donor is available.

TA604 Idelalisib for treating refractory follicular lymphoma

In 2019, NICE assessed cost-effectiveness of idelalisib, used as monotherapy for refractory follicular lymphoma, a malignancy of B-lymphocytes. Idelalisib is a kinase inhibitor, reducing the activity of phosphoinositide 3-kinase p110δ (PI3Kδ), which is an enzyme involved in growth, proliferation, differentiation and survival of blood cells. PI3Kδ is known to be overactive in B-cell malignancies, and is therefore used as therapeutic target in follicular lymphoma. Gilead was the submitting company, and Kleijnen Systematic Reviews produced the Evidence Review Group (ERG) report.

The single-arm main trial (DELTA) was supplemented with data from the Compassionate Use Program: *The company supplemented the DELTA study with another source of evidence for idelalisib: the Compassionate Use Programme (CUP). This provided retrospective observational data from patients with follicular lymphoma having compassionate treatment in the UK and Ireland. The company took a subset of 79 patients with relapsed or refractory follicular lymphoma that had been treated with idelalisib. In these patients, median progression-free survival was 7.1 months, and median overall survival was not reached.*

The Committee decided that neither data set was '*adequate enough for using to determine how well patients on idelalisib fared compared with people who had not taken idelalisib.*' Despite the absence of controlled trials, the committee discussed the evidence presented to determine which set (trial or CUP) was most generalizable to the use of idelalisib clinical practice. Evidence was ambivalent:

- *The committee noted the difference in Eastern Cooperative Oncology Group (ECOG) performance status and Follicular Lymphoma International Prognostic Index (FLIPI) I and II scores between DELTA and the CUP. Notably, 8% of patients in DELTA had an ECOG score of 2 to 4 compared with 25% of patients in the CUP, reflecting poorer performance among patients in the CUP. The clinical experts stated that the ECOG performance status in CUP more closely reflected clinical practice than that in DELTA.*
- *The clinical experts noted that the time since completing the last therapy was shorter in DELTA than in the CUP, suggesting that patients in DELTA had a poorer prognosis*

Resulting in the ambivalent conclusion that *'the populations in DELTA and the CUP were different. (…) Also, patient and disease characteristics at baseline differed, with some suggesting a more favourable prognosis in DELTA than in the CUP, and others suggesting the opposite.' Even help from clinical experts could not resolve the issue, as 'the clinical experts suggested that the CUP cohort was more likely to reflect the intended UK treatment population because it was a 'real-world' study with*

patients from Britain and Ireland. However, the clinical experts acknowledged that such studies lack the methodological rigour typical of a clinical trial.' In the end, '*The committee concluded that it was unclear whether the DELTA population or the CUP cohort more closely reflected clinical practice and took both into account for decision making.*'

Idelalisib was not recommended in the Final Appraisal Determination. '*There are a wide range of cost-effectiveness estimates but, because the evidence is weak, idelalisib is not considered to represent a cost-effective use of NHS resources. Therefore, idelalisib cannot be recommended for routine use in the NHS.*'

CHAPTER 7

Results from expanded access programs: a review of academic literature

Polak TB, Cucchi DGJ, Schelhaas J, Ahmed SS, Khoshnaw N, van Rosmalen J, Uyl-de Groot CA.
Drugs. 2023 Jun;83(9):795-805

ABSTRACT

Background Although expanded access is an increasingly used pathway for patients to access investigational medicine, little is known on the magnitude and content of published scientific research collected via expanded access.

Methods We performed a review of all peer-reviewed expanded access publications between January 1st 2000 and January 1st 2022. We analyzed the publications for drugs, diseases, disease area, patient numbers, time, geographical location, subject, and research methodology (single-center/multicenter; international/national; prospective/retrospective). We additionally analyzed endpoints reported in all COVID-19-related expanded access publications.

Results We screened 3,810 articles and included 1,231, describing 523 drugs for 354 diseases for 507,481 patients. The number of publications significantly increased over timeppp ($p < 0.001$). Large geographical disparities existed as Europe and the Americas accounted for 87.4% of all publications, whereas Africa only accounted for 0.6%. Oncology and hematology accounted for 53% of all publications. Twenty-nine percent of all expanded access patients (N=197,187) reported on in 2020 and 2021 were treated in the context of COVID-19.

Conclusion By summarizing characteristics of patients, diseases, and research methods described in all scientific literature published on expanded access, we provide a unique data set for future research. We show that published scientific research on expanded access has surged over the past decades, partly due to COVID-19. However, international collaboration and equity in geographic access remain an issue of concern. Lastly, we stress the need for harmonization of research legislation and guidance on the value of expanded access data within real-world data to improve equity in patient access and streamline future expanded access research.

INTRODUCTION

Patients who cannot be adequately treated with marketed therapies and who simultaneously are unable or ineligible to enroll in clinical trials may seek different means of accessing unlicensed treatments. Legislators have created 'expanded access' pathways to allow these patients to access unregistered medicines.[64] The United States (US) Food and Drug Administration (FDA) institutionalized 'expanded access' in 1987 in efforts to provide more treatment options for AIDS patients.[4] The European Medicines Agency (EMA) has drafted Guidance on Compassionate Use in 2007, but individual members states of the European Union (EU) have a longer history of individually regulating national 'expanded access pathways' and still retain that freedom today.[65]

The primary intent of expanded access programs is to provide treatment access, which contrasts with the primary intent of research in clinical trials. Nonetheless, there is an increasing interest in simultaneously providing access whilst collecting, analyzing, and disseminating results from expanded access usage. First, these data may further estimate treatment patterns and outcomes in non-trial (e.g., 'real-world') patients.[51,52] Second, including expanded access may increase statistical precision simply by increasing patient numbers - this pertains particularly to expanded access use of rare diseases drugs.[11,66] While various regulators in the EU and US mandate some form data collection during expanded access, others restrict or even prohibit the collection and subsequent analysis.[66] To date, opinions differ to which extent data collection under expanded access is feasible, desirable, and reliable.

The evidence that stems from expanded access has been used to inform safety and efficacy labels by regulatory bodies such as the FDA and EMA.[50] Furthermore, data from expanded access are incorporated by health technology assessment bodies to determine cost-effectiveness of novel therapies in the United Kingdom, the Netherlands, the United States, and France.[67] To what degree data from expanded access of investigational medicine are published in academic literature remains unknown. A mapping of expanded access scholarship with regards to time, location, subject, research methodology, and authorship is lacking. There is no information on which drugs are used in expanded access literature, by how many patients, for which diseases, and where such expanded access programs take place.

Here, we examine to which extent research on expanded access is disseminated in the academic literature. Furthermore, we analyze the type, subject, and participants within such research. We identify disparities in scientific research across geographies and disease areas and discuss the resultant issue of access inequality. Lastly, we provide recommendations on the harmonization of expanded access research in the future and facilitate such research by the data set created in this work.

METHODS

We conducted a review of all publications indexed in MEDLINE through PubMed that report original results of expanded access usage. We included all peer-reviewed literature that was published between the 1st of January 2000 and the 1st of January 2022. All articles that included any term related to expanded access (e.g., compassionate use, pre-approval access, managed access, special access) were considered.[2] We relied on the self-assessed classification of expanded access by the authors and removed all instances with an erroneous expanded access classification, e.g., off-label use and clinical trials, where possible. The detailed search protocol is available in the Supplementary Material.

Citation and review management

All citations were exported from PubMed in EndNote Version 19 (Clarivate, London, United Kingdom), where duplicates and publications without full text were detected and removed. Citations were subsequently uploaded in Rayyan, an online systematic review platform.[68] TBP, DGJC, NA, and SSA independently conducted the review – all records were reviewed at least twice. A random sample of 100 articles was additionally assessed by a third independent reviewer.

Eligibility, screening, and labeling

Based on the titles and abstract, we labelled articles for 'inclusion', 'exclusion', or further investigation ('unknown'). Articles labelled 'unknown' or where reviewers disagreed on inclusion/exclusion were further assessed by reading the full text. If the third reviewer was unsure, remaining disagreement was solved through discussion of the full text with a fourth author. Exclusion reasons included:

1. Non-English literature
2. Not relevant (topic is not expanded access, e.g., off-label use or formal clinical trials)
3. Not primary research
    - Errata, editorials, replies
    - News articles
    - Meta-analyses, guidelines, systematic reviews
4. Not disseminating investigational results of pharmaceutical therapeutics
    - Devices, procedures
    - Other research topics (e.g., legal/ethical/policy issues)

Subsequently, we analyzed the full text articles for pre-defined main outcomes: time of publication, research location (country, national/international, single-center/multi-center), number of patients, research methodology (retrospective/prospective), drug, disease, and disease area. To provide the reader with insights that cannot be generalized across disease areas, and since expanded access gained particular attention during the COVID-19 pandemic, we specifically provide more detailed information on all COVID-19 related expanded access articles, including systematic analysis of all end points used (see Supplementary Material).

Our screening procedure was tested on 50 abstracts prior to the start of the review. The detailed protocol is provided in the Supplementary Material. To give the reader more insight into the content of expanded access publications, we describe ten randomly selected articles in detail in the Supplementary Material. We cover the expanded access research setup, patient numbers, intervention, outcomes, and author interpretation of the results, including comparison with formal clinical trial results.

Data management and statistics

A chart was created in Excel 2010 (Microsoft, Redmond, WA) to tabulate the main outcome characteristics. We subsequently analyzed the data in R version 4.0.1 (PBC, Boston, MA), and code was generated to detect implausible values that were subsequently examined by the reviewers. The code to replicate this study is available on the GitHub of the first author.[12] We used descriptive statistics to summarize our findings. To detect trends across time in the number of publications, we used a Spearman rank correlation test with a two-sided significance level of 0.05.

RESULTS

We examined 3,820 publications. After removing duplicates (n=10) and articles without full text (n=32), we screened 3,778 records for eligibility. We excluded articles not written in English (n=184) and not concerning expanded access (n=1,333). Finally, errata, replies, and editorials (n=101), news articles (n=50), or meta-analyses, systematic reviews, and guidelines (n=478) were removed. This led us to a collection of primary research on expanded access. We further removed non-pharmacological therapeutic articles, e.g., research on devices and procedures (n=133), and research on the legal, ethical, or policy aspects of expanded access (n=150). A schematic overview can be found in Figure 7.

12 https://github.com/TobiasPolak/

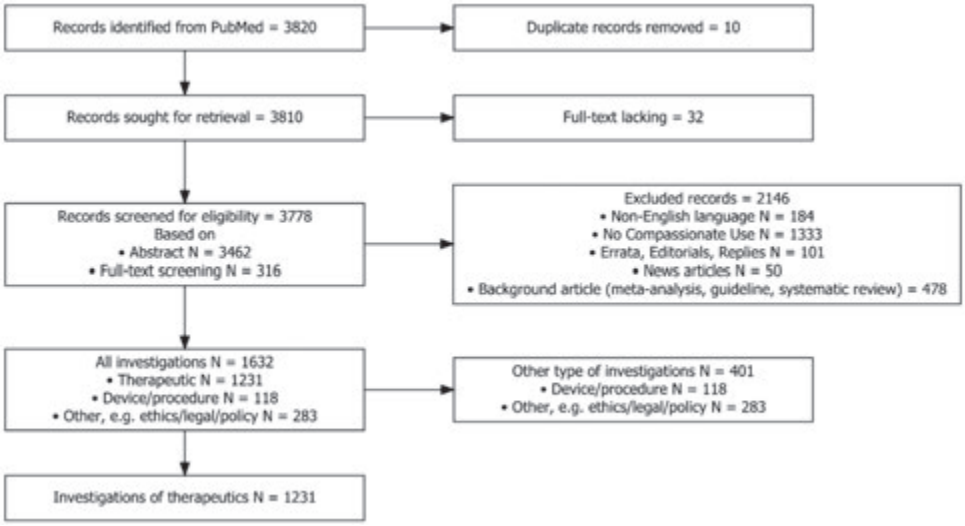


Figure 7: Workflow diagram of the review.

The reviewers agreed directly in 89.2% of the cases. Three reviewers reviewed 10.4% of cases and four reviewers reviewed 1.5% of all cases (including a random sample review of 100 articles). TBP reviewed all 3,810 publications, followed by DGJC (N=1,847), SSA (N=1,843), and NK (N=631). The review was conducted in May and June 2022.

The number of publications over time is depicted in Figure 8. We observe an increasing trend over time: from 12 therapeutic investigations in 2000 to 175 in 2021, (ρ= 0.96, $p < 0.001$).

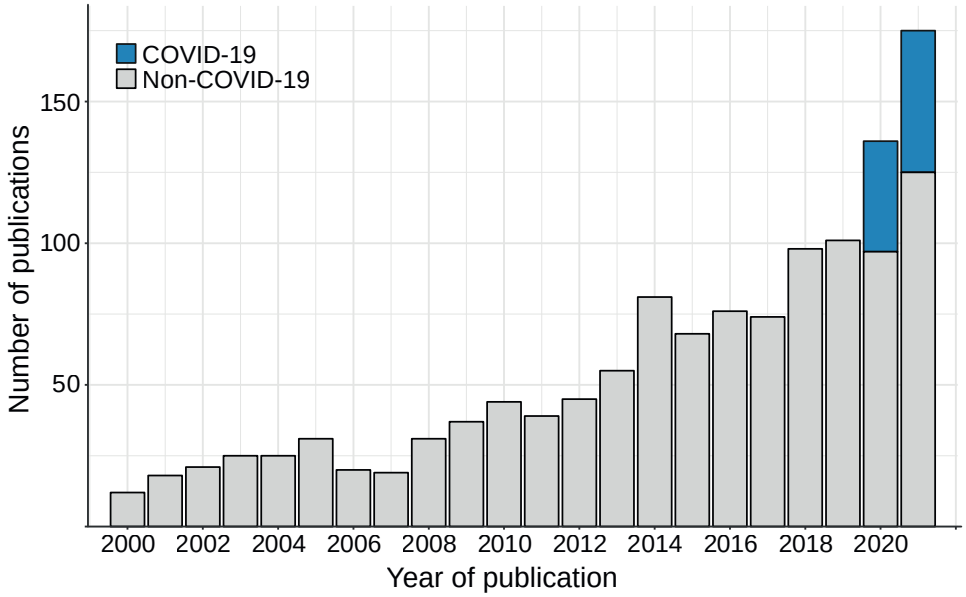


Figure 8: Bar chart of the absolute number of peer-reviewed expanded access publications of therapeutic investigations over time.

The descriptive statistics are provided in Table 3. The median number of patients described was 43, but this number varied widely, ranging from N=1 in case reports to N= 95,000. Case reports comprised almost one in eight (12.3%) publications. Of the non-case-report publications (i.e., N>1), the median number of patients was 57, with an interquartile range (IQR) of 18 to 198 patients. Most of the data had been collected retrospectively (51%), and only 12.1% (149/1,231) of all publications were international collaborations. For national (single-country) publications (n=1,082), the majority (51.1%) were collaborative publications between multiple hospitals. Most studies only included adults; 22% included mixed populations with both adults and children, or children only. Researchers in the US generated the most publications in absolute terms (22.1%, 240/1,082), followed by Italy (16.9%, 183/1,082) and France (8.3%, 90/1,082), see Table 4**.** When we calculated the number of publications relative to the average populations (in millions) from these countries during the midpoint of the time period (2006-2016), Italy had the highest output per capita with 3.1 articles per million inhabitants. Italy is followed by Belgium and Spain with a relative publication output of 2.5 and 1.8 per million inhabitants, respectively. Table 4 shows the geographic distribution of the top ten most productive regions in terms of expanded access publications. Europe and the Americas accounted for 87.4% of all publications, whereas Africa only accounted for 0.6%. High-income regions (North/South/West Europe and Northern America) comprised 82.5% percent of all publications and 92.4% of all patients described in our data set (Figure 9).

Table 3: Descriptive statistics of expanded access publications included in this review.

Variable	Overall, N = 1,231[1]	Publication Collaboration International, N = 149[1]	National, N = 1,082[1]
Number of patients included in report			
Mean (SD)	413 (3,161)	881 (1,743)	348 (3,304)
Median (25%; 75%)	43 (8; 149)	239 (37; 1,032)	37 (6; 113)
Minimum; Maximum	1; 95,000	3; 14,204	1; 95,000
Case report			
No, N>1	1,077 (88%)	149 (100%)	928 (86%)
Yes, N=1	152 (12%)	0 (0%)	152 (14%)
Single- or multicenter			
Multicenter	702 (57%)	149 (100%)	553 (51%)
Single center	479 (39%)	0 (0%)	479 (44%)
Not described	50 (4.1%)	0 (0%)	50 (4.6%)
Methodology			
Retrospective	626 (51%)	51 (34%)	575 (53%)
Prospective	495 (40%)	81 (54%)	414 (38%)
Not described	110 (8.9%)	17 (11%)	93 (8.6%)
Includes pediatric patients			
No	892 (72%)	97 (65%)	795 (73%)
Yes	266 (22%)	47 (32%)	219 (20%)
Not described	73 (5.9%)	5 (3.4%)	68 (6.3%)

[1]n (%). SD, standard deviation.

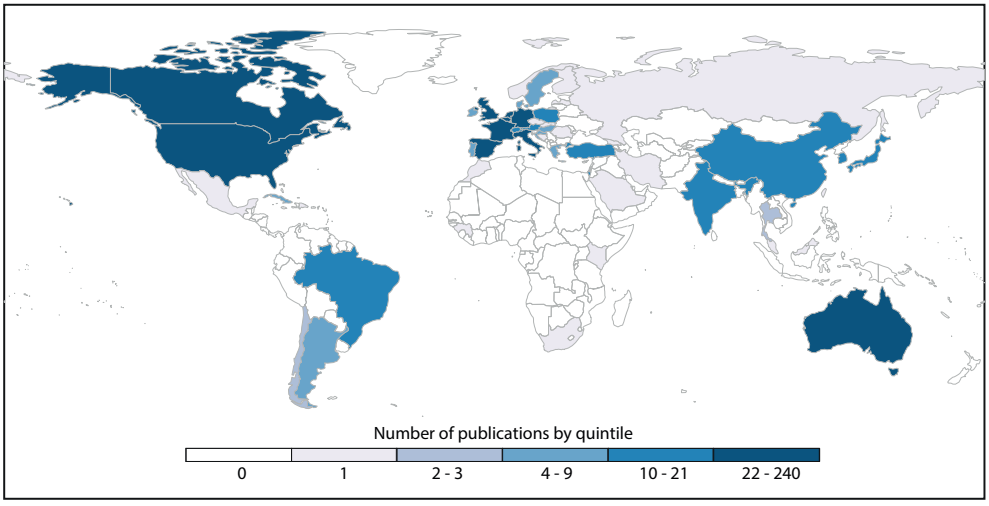


Figure 9: Global distribution of number of peer-reviewed expanded access publications, by quintile.

As the results described in this section aim to abstract information across drugs and conditions, the reader that is interested in a more detailed description of expanded access publications can find an analysis of ten randomly selected articles in the Supplemental Material. This sample demonstrates the heterogeneity of our dataset across a variety of quantitative variables such as sample size, study design, geographic region, patient populations, and EAP duration. But the articles also differ on qualitative aspects. Some authors discuss at length the differences between the patients in the EAP and the clinical trials and how these differences may result in different outcomes. Other authors are unable to report on such trial versus EAP differences, as disparities in sample sizes may prevent a useful comparison (e.g., case report). Additionally, trial results may simply be unavailable for the product while expanded access was provided as trials might have been ongoing or not even initiated.

Table 4: Characteristics of top ten most productive countries of national expanded access publications, ranked by the number of publications. US, United States. *, average population between 2006 – 2016.

Country	Publications	Patients	Population*	Publications per capita
US	240	230,566	311.3	0.8
Italy	183	39,100	59.6	3.1
France	90	24,250	65.3	1.4
Germany	88	6,473	81.5	1.1
Spain	83	6,048	46.2	1.8
UK	49	2,945	63.2	0.8
Canada	32	11,736	34.4	0.9
Australia	29	2,599	22.4	1.3
Netherlands	29	3,622	16.7	1.7
Belgium	28	5,869	11.0	2.5

Disease areas

The 1,231 publications covered 354 unique diseases across 18 disease areas. The top ten most frequently appearing disease areas are depicted in Figure 10. The two largest areas, oncology 39.6% (488/1,231) and hematology 13.8% (170/1,231), are further broken down per top ten most frequent diseases. Note that a single publication can cover multiple diseases (this is the case in 38 publications), for example where a single drug is tested in adjacent diseases, such as expanded access of azacitidine to treat patients with both acute myeloid leukemia and myelodysplastic syndromes.[69–71] Other instances include diseases sharing a common actionable target such as ErbB2/HER2 in breast and colorectal cancer and malignant melanoma.[72]

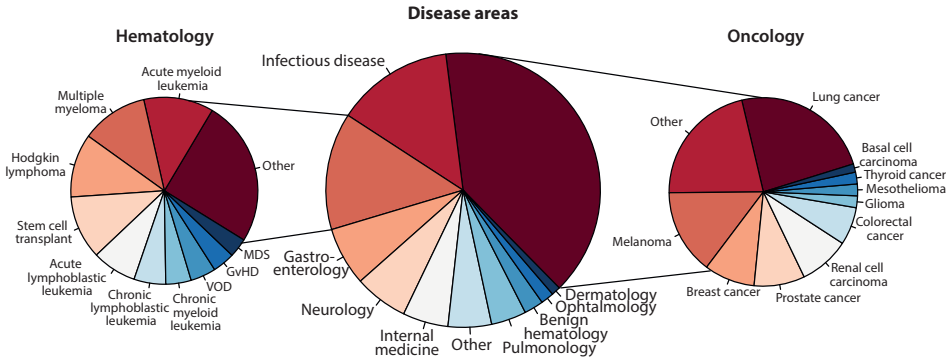


Figure 10: Distribution of disease areas covered by expanded access literature from 2000 – 2021. MDS, myelodysplastic syndromes. GvHD, Graft-versus-Host Disease.

Pharmacological therapeutics

A total of 523 unique pharmacological therapeutics were described in our data set. Eighty-seven publications covered more than one therapeutic. The top ten most frequently appearing drugs are depicted in Table 5. Nivolumab was the most frequently appearing drug, likely due to its use in a variety of solid tumors (non-small cell lung cancer, glioblastoma, renal cell carcinoma) and non-solid tumors (Hodgkin lymphoma), as well as its use in combination therapy for melanoma with ipilimumab. There may also be one drug-indication pair featuring a multiplicity of publications. In the case of cabazitaxel, a chemotherapy for castrate-resistant prostate cancer, there are individual expanded access publications from single centers,[73] various single-country publications in Europe,[74–76] as well as a Europe-wide publication.[77] Furthermore, these 15 publications focus on different aspects of the treatment, such as safety,[78] or quality-of-life.[79]

The effects of the COVID-19 pandemic

The steep increase in publications in recent years can partially be attributed to COVID-19 pandemic. In 2020 and 2021, a large portion of publications was dedicated to medicine that could potentially treat COVID-19 infections: 29% (39/136) in 2020 and 29% (50/175) in 2021. Similarly, 49% (87/176) of expanded access publications on infectious diseases are related to COVID-19.

Table 5: Overview of top ten most frequently described pharmacological therapeutics.

Drugs	Publications	Patients	Disease entities
Nivolumab	48	15,957	Lung Cancer (26x, N=12,327), Renal Cell Carcinoma (7x, N=2,062), Melanoma (5x, N=1,073), Hodgkin Lymphoma (4x, N=259), Basal Cell Carcinoma (1x, N=1), Gastric Cancer (1x, N=113), Germ Cell Tumors (1x, N=7), Glioblastoma (1x, N=1), Hemophagocytic Lymphohistiocytosis (1x, N=7), Mesothelioma (1x, N=107)
Ipilimumab	37	8,244	Melanoma (37x, N=8,244)
Gefitinib	36	3,900	Lung Cancer (34x, N=3,834), Head and Neck Cancer (2x, N=66)
Sofosbuvir	21	2,751	Hepatitis C (20x, N=2,749), Yellow Fever Virus (1x, N=2)
Sunitinib	18	23,996	Renal Cell Carcinoma (14x, N=23,964), Colorectal Cancer (2x, N=30), Liposarcoma (1x, N=1), Sarcoma (1x, N=1)
Everolimus	17	8,074	Renal Cell Carcinoma (4x, N=4,193), Neuroendocrine Tumors (3x, N=416), Breast Cancer (2x, N=3,282), Epilepsy (2x, N=16), Basal Cell Carcinoma (1x, N=4), Hodgkin Lymphoma (1x, N=33), Paraganglioma; Pheochromocytoma (1x, N=4), Renal Angiomyolipomas Tuberous Sclerosis Complex (1x, N=19), Subependymal Giant Cell Astrocytoma Associated With Tuberous Sclerosis (1x, N=100), Tuberous Sclerosis (1x, N=7)
Plerixafor	17	1,378	Stem Cell Transplant (17x, N=1,378)
Cabazitaxel	15	4,925	Prostate Cancer (15x, N=4,925)
Cannabidiol	15	2,148	Epilepsy (12x, N=1,446), Dravet Syndrome & Lennox-Gastaut Syndrome (2x, N=700), Dravet Syndrome (1x, N=2)
Cefiderocol	15	163	COVID-19 (2x, N=124), Osteomyeleitis (2x, N=2), Pseudomonas Aeruginosa (2x, N=2), Acinetobacter Baumanii Infections (1x, N=3), Aortic Valve Endocarditis (1x, N=1), Bacteriemia (1x, N=13), Carbapenem-Resistant (Cr) Gram-Negative Pathogens (1x, N=13), Enterobacter Hormaechei Infection (1x, N=1), Klebsiella Pneumoniae (1x, N=1), Multidrug Resistant Bacterial Infections (1x, N=1), Pancreatic Abscess (1x, N=1), Prosthetic Joint Infection (1x, N=1)

The pandemic boosted publications on potential treatments such as convalescent plasma (N=15), remdesivir (N=14), and tocilizumab (N=11). The publications on the use of convalescent plasma to potentially treat COVID-19 infections comprised 194,256 patients, shifting the distribution of patient numbers on its own. We systematically extracted and grouped all end points reported in COVID-19 related publications. The 42 unique endpoints are not limited to mandatory safety monitoring: The five most frequently described endpoints in COVID-19 publications were Adverse Events (57%), mortality (45%), inflammatory markers (34%), oxygen support (32%) and clinical improvement (26%) (Table 6, see Supplementary Material for a complete overview of all used endpoints). In total, 41 unique drugs have been provided under compassionate use to treat COVID-19. Of these, four drugs received EMA approval, and five drugs are authorized for use by the FDA (in part under Emergency Use), as of January 2023.[80] The submission to the EMA for the FDA-approved agent baricitinib was withdrawn by the applicant.[81]

Table 6: Top ten endpoints reported in COVID-19 related expanded publications.

Endpoint	Occurrence (%) of articles	Terms used in the publications
Adverse Events	57	Adverse events, TESAEs, Serious adverse events, abnormal laboratory measurements (primarily regarding liver function, e.g., ALT, AST)
Mortality	45	All-cause 28-day mortality, survival, crude mortality, death, mortality rate
Inflammatory markers	34	IL-6, pro-inflammatory biomarkers, NK-cell count, leukocyte counts, immune monitoring, cytokine response, inflammatory mediators, biomarkers associated with complement activation, CRP, fibrinogen, D-dimer, urea, ferritin, LDH
Oxygen support	32	Oxygen requirement, supplemental oxygen, return to room air (RTRA), oxygenation
Clinical improvement	26	SAPS II score, multi organ dysfunction score (MODS), disease severity score, clinical improvement meeting the discharge criteria, physician-reported clinical status, successful clinical outcome, clinical recovery, clinical status, clinical cure, Sepsis-related Organ Failure Assessment (SOFA) Score
Hospital discharge rate	26	Hospital discharge rate, duration in hospital, days in hospital
Laboratory values	25	Biochemical parameters, blood values, chemistry, clinical chemistry parameters, hemoglobin, and platelet count + complete blood count, coagulation + hematology parameters, ABT, ALT, AST, liver function
Viral load	24	SARS-Cov-2 negative conversion, COVID-19 PCR, COVID-19 serum antibody tests, COVID-19 viral load, microbiological cure
Radiological change	20	Tayler's scale, radiological findings, Computed Tomography findings, lung opacities, ground class opacities, patchy opacities
Respiratory support	20	Ventilated, mechanical ventilation, ventilator-free days, respiratory function, respiratory improvement, extra-corporeal membrane-oxygenation (ECMO)

Abbreviations: ABT antibody titer, ALT alanine aminotransferase, AST aspartate aminotransferase, CRP C-reactive protein, ECMO extracorporeal membrane oxygenation, IL-6 interleukin 6, LDH lactate dehydrogenase, MODS multiorgan dysfunction score, NK natural killer, PCR polymerase chain reaction, SAPS simplified acute physiology score, SOFA sepsis-related organ failure assessment, TESAEs treatment-emergent serious adverse events.

DISCUSSION

In this paper, we have mapped the landscape of expanded access publications from January 1st 2000 to January 1st 2022. To the best of our knowledge, this is the first literature review of expanded access publications to assess drugs, diseases, patient numbers, and research methods. We have identified 1,632 original investigations of expanded access, of which 1,231 focus on pharmacological therapeutics, and the number of publications increases significantly over time. The increase in publications reflects a general increase in attention for expanded access, as reported by regulators, industry, and through other scholarship. Our work provides the first annotated data set that yields insights into how many patients contributed to the peer-reviewed scientific literature through expanded access programs, across diseases, across geographies, and across drugs.

The geographic distribution of expanded access publications highlights the disparity of availability of investigational medicine. High-income countries produce more publications compared with low-income countries, which may be partly explained by excluding non-English literature, but may also be attributed to manufacturer and scientific willingness to provide expanded access and facilitate subsequent research. Our findings reflect the limited access to medicine in developing countries in general, but to investigational medicine in particular – an issue worth exploring in future research.

The differences between countries within the European Union may be due to differences in regulatory preferences. Italy, with the highest number of publications per capita, is more liberal in allowing data collection compared with countries such as Sweden and Finland.[65] The variance in allowing expanded access programs to generate evidence among European regulators has created a maze of national pathways for manufacturers to navigate.[66] Such complexity may provoke reluctance from drug manufacturers to provide expanded access in the first place, which may impede rather than facilitate equity in patient access.

The largest share of expanded access research is devoted to oncology and (malignant) hematology, accounting for 53.5% publications. This is driven in part by the large unmet medical need of cancer patients, as well as the abundance of trials in these areas. Furthermore, regulators offer specific guidance for expanded access to oncology (for example, through the FDA's Project Facilitate),[82] educating oncologists and expediting access to anti-cancer drugs.

Our findings seem to support the position that, indeed, expanded access programs can be used to collect data that can further the knowledge of an investigational medicine. The stance of some regulators (e.g., Sweden, Finland, Canada) that data collection within an expanded access

program is prohibited (or discouraged), in part over fears of data quality or companies attempting to bypass trial regulations,[65,83,84] seems to be at odds with the numbers of publications from those countries (n=13, n=5, n=56, respectively). The number of expanded access publications show that the treatment of patients with investigational medicine is, in itself, being used as a means to support (ongoing) investigations.

Nonetheless, the analyses of expanded access data should be interpreted with caution. Expanded access data are non-blinded, non-randomized data, and as such may be inherently confounded. These 'real-world' data may harbor serious data quality issues. Furthermore, expanded access data may suffer even more quality loss as 50.9 % of the reports in our sample collected data retrospectively. This may severely impact data quality, although main parameters (such as survival) should be straightforward to gather. In our analysis of endpoints used in EAPs for COVID-19, we found that data is collected beyond mandatory safety reporting. Endpoints included various clinical improvement ratings/scales, respiratory or oxygen support status, duration of hospitalization, viral load, and patient-reported outcomes among others. The heterogeneity of research methods and endpoints makes it difficult to compare studies.

Ideally, an EAP should include a pre-specified, prospective data collection to ensure highest data quality that is fit-for-purpose. Although the inclusion of expanded access data (and other sources of real-world data) in regulatory decision-making is increasing,[50,85,86] the lack of oversight could contribute to suboptimal data quality and hesitance of regulatory bodies to include said data in decision-making processes. To expand the application of expanded access data beyond peer-reviewed publications, it is important to develop minimal data quality standards for expanded access studies in the future.[87]

Harmonization of publications may be an area of potential development. Some expanded access programs harbor 'salami-tactics': i.e., there are different publications per center, then per region, then per country, and subsequently, a synthesized international publication.[73–77] Additionally, the basis of a new publication may not be a different geographic location, but rather a different (sub) topic: publishing separately on safety,[78] efficacy, and/or quality-of-life.[79] Although we acknowledge that the lack of observational research harmonization across countries impedes international collaboration, we question the incremental added value of each of these single publications as opposed to several large, overarching, international publications. As local investigators may not be aware of all scientific endeavors worldwide, drug manufacturers should better coordinate local efforts by connecting researchers across regions.

The impact of COVID-19 on the expanded access landscape is remarkable. Early in the pandemic, various authors cautioned against the widespread use of medication outside of clinical trials as

randomized trials would be 'the only way to find effective and safe treatments for COVID-19'.[83] Indeed, the results from the large-scale expanded access program of convalescent plasma in the US later failed to replicate in various randomized trials.[88–91] Although we agree that the place for expanded access is in addition to clinical trials rather than instead of, there is a place for expanded access in facilitating serendipitous findings, especially in the field of rare diseases. Evidence of expanded access can be used in addition to clinical trials to explore the safety and effectiveness of medicines used in different populations, or in (slightly) different indications (for example, in the case of cancer therapies targeting the same genetic aberration in a different histology). The drawback of expanded access data collection does not imply that these data are worthless or that no data ought to be collected: we, together with other scholars,[11,52] believe that the treatment of a patient with investigational medicine should always be used to further the understanding of the potential benefits and risks of investigational medicine.[87]

Limitations and future research

First, we attempted to differentiate expanded access programs from other types of access to unregistered products, such as trials, compounded medication, or off-label usage. To label a paper as 'expanded access' or not, we primarily relied on the self-reported use of 'expanded access', i.e., if the authors (and editors, peer-reviewers) approved the term 'expanded access'. Nonetheless, an exact definition of expanded access varies per jurisdiction. A strict interpretation of expanded access is 'non-trial access to pre-approval medicine'– yet these programs can also be used after a product has been withdrawn from the market (post-withdrawal rather than pre-approval), or to bridge the gap between marketing authorization and reimbursement (post-approval, pre-reimbursement). In addition, the term expanded access is sometimes used to denote off-label usage or 'compassionate use trials'. To prevent erroneous inclusion of (randomized) trials or off-label usage, we used an independent review process and deliberated in case of doubt. Note that the interchangeable usage of expanded access and off-label is not wrong per se: some countries employ the same terminology and pathways for expanded access as for off-label usage. Most forms of off-label usage differ considerably from 'expanded access', in other instances, these concepts may be inherently related.

Second, we only focused on peer-reviewed publications indexed in PubMed that were written in English and included 'expanded access' related terms. As such, we have missed both non-English publications and literature that did not incorporate these terms. Other ways of disseminating expanded access results, such as posters or oral presentations at scientific conferences have not been investigated in our work. The use of additional databases (e.g., Embase) could have resulted in more publications. Therefore, our work may underestimate the number of expanded access publications, drugs, and patients over the past two decades. Furthermore, not all expanded access

programs will result in publications, and the number of publications is potentially only a proxy for the total number of expanded access programs.

Further research could focus on the bias (quality) of expanded access publications or could further explore differences between trial and expanded access publications. This concerns both patient demographics, i.e., are 'expanded access patients' really more 'real-world' than trial patients?, as well as clinical outcomes, i.e., are expanded access patients potentially worse off than trial patients?

Conclusion

The increasing interest in access to investigational medicine is reflected by a rise in the number of publications of expanded access programs from 2000-2019 and amplified by the COVID-19 pandemic through 2020 and 2021. The 1,231 publications identified in this review shed a novel light on the characteristics of patients, diseases, and research methods of expanded access programs. Harmonization of research legislation and guidance on the value of expanded access data within real-world data frameworks should ensure that patients in expanded access programs globally contribute efficiently to scientific evidence.

SUPPLEMENTARY MATERIAL

Review Protocol

This Review Protocol is based on a template from JBI Evidence Synthesis.[13]

Reviewers: Tobias B. Polak, David G.J. Cucchi, Jasmin Schelhaas, Syed S. Ahmed, Naima Khoshnaw

Objective: The objective of this scoping review is to understand the literature landscape of compassionate use research by quantifying and analyzing research papers with compassionate use data.

Introduction: Access to medicine – and faster access to investigational medicine in particular – has become a topic of increasing interest and debate. Is it unclear how often compassionate use data have been used in scientific literature and for what type of studies.

Inclusion criteria: We included all (peer-reviewed) publications that are indexed on MEDLINE via PubMed with compassionate use (or related terms) included in the text.

Methods: We searched MEDLINE (via PubMed) from January 1st, 2000, to December 31st, 2021. The search was conducted in February - June 2022 and included English publications on compassionate use.

13 https://jbi.global/scoping-review-network/resources

Introduction

Note – below introduction and text is copied and adjusted from the template of JBI Evidence Synthesis from Literature Reviews[1], as well as based on previous articles from TBP.

A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, PROSPERO, and *JBI Evidence Synthesis* was conducted and no current or underway systematic reviews or scoping reviews on the topic were identified.

Expanded access (EA) is a pathway for patients who suffer from life-threatening conditions, who cannot enter clinical trials, and have exhausted all approved treatment options, to access investigational medicine (i.e., medicines that are not regulatory approved and are still experimental).[4] It is also known as 'compassionate use', 'early access' or 'non-trial pre-approval access'.[2] The primary intent of EA programs is to provide patients and physicians in dire need with potential treatment options outside of clinical trials. Secondary, such programs may be used to collect RWD. It offers a potential opportunity to collect real world data in a pre-approval setting.[51,52]

Data from EA programs (EAPs) are used increasingly by regulators such as the US Food and Drug Administration and the European Medicines Agency in regulatory decision-making (i.e., to determine whether a drug should be recommended for routine use for a distinct disease and patient population).[50] Furthermore, a recent overview of health technology appraisals by the English national institute for cost-effectiveness studies (NICE) concluded that 20% of these appraisals include data from EAPs. It is unknown if, how often and how data from EAPs are disseminated through scientific literature by medical companies or researchers. In this scoping review, we sought to quantify and classify the landscape of scientific literature on compassionate use.

Main review question

How does compassionate use (data) contribute to research literature?

- How many original studies reporting data originating from EAPs have been published?
  - Does this vary between disease area, disease, drug type, country, time, etc.
- What studies are published on the collection, regulations on and use of expanded access data?

Keywords

Compassionate Use; Real-World Data; Health Policy; Expanded Access

Eligibility criteria

We will include publications where the main data source or the main theme is expanded access (data). These must have been published between 01-01-2000 and 01-01-2022.

Methods

The study will be conducted via Rayyan. All records will be assessed by two reviewers independently. If there is disagreement, a third reviewer and potentially fourth reviewer will assess the records. The researchers will be assigned random records. TBP is expected to review all records at least once.

Search strategy

We will search through PubMed for all articles with expanded access terms.[2] We will exclude all articles published prior to 1st of January 2000 and after 1st of January 2022. PUBMED:

'compassionate use trials'[MeSH Terms] OR 'expanded access'[All Fields] OR 'early access'[All Fields] OR 'managed access'[All Fields] OR 'special access'[All Fields] OR 'named patient'[All Fields] OR 'single patient IND'[All Fields] OR 'compassionate use'[All Fields] OR 'compassionate study'[All Fields] OR 'pre approval access'[All Fields]

Study/Source of Evidence selection

Following the search, all identified citations will be collated and uploaded into EndNote Version 19 (Clarivate, London, UK) and duplicates removed. Following a pilot test with 50 records, titles and abstracts will then be screened by two or more independent reviewers for assessment against the inclusion criteria for the review. The full text of selected citations will be assessed in detail against the inclusion criteria by two or more independent reviewers. Reasons for exclusion of sources of evidence at full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion and an independent additional review of a third reviewer. We will also conduct a random sample of 100 articles that will be checked by an additional reviewer (e.g., third or fourth).

Inclusion

We will include all articles with compassionate use as main theme, such as disseminations of individual expanded access programs or named-patient cases, or overview of regulatory hurdles.

Inclusion Grounds	Label
Original investigation, dissemination of results, etc	investigation
Overview articles (ethics, regulatory, etc)	review
Opinion articles	opinion

Additional label for remarkable cases: funny or interesting; case-report
Additional label for cases where the full text has been read to decide: full text read

Exclusion

We will exclude publications on the following reasons. Please make sure to add these labels manually and exactly to Rayyan.

Exclusion Grounds	Reason
Not compassionate use, e.g., off-label use or clinical trial.	exclude
News articles on compassionate use	news
Background articles (eg drug history, meta-analyses)	Background article (already default)
Publications without full text	full text lacking
Errata, replies, editorial	errata, replies, editorials
Non-English literature	foreign language (already default)

Data extraction

We will collect information across the following outcomes in a chart in Excel.

Parameter	Source
Time of publication	Journal article
Country	Methods section. Search for 'international / national' and 'ethics'.
Single-center/multicenter	Methods section. Search for 'institution/center/hospital'
Number of patients	Results section (see Table 1). In case of multiple populations, select all unique patients that received at least one round of treatment.
Methodology	Methods section. Search for 'retrospective, prospective, chart review'
Drug	Abstract and Methods. Will be classified by DGJC (physician)
Disease	Abstract and Methods. Will be classified by DGJC (physician)
Disease area	Based on Disease. Will be classified by DGJC (physician)

If values are not (clearly) reported, please select 'not-reported' for these values.

DGJC (physician) will be manually curating the disease and drug lists by sorting them in alphabetic order and assessing the total list of unique disease and drug names. We will specifically emphasize the articles with Disease == 'Covid-19'.

Categorization of endpoints in COVID-19-related expanded access publications.

Methodological approach

1. Text search for 'Outcomes' or 'endpoints'. In case not found, proceed to step 2.
2. Manual assessment of Abstract and conclusion. In case not found, proceed to step 3.
3. Manual assessment of 'Methods' and 'Results' section.
4. For Case reports, we only assessed measurements that were performed during or following treatment with expanded access medication.
5. Identified terms were grouped when similar according to the Table below.

Category	Included terms
Viral load	SARS-Cov-2 negative conversion, COVID-19 PCR, COVID-19 serum antibody tests, COVID-19 viral load, microbiological cure
Mortality	All-cause 28 day mortality, survival, crude mortality, death, mortality rate
Hospital discharge rate	Hospital discharge rate, duration in hospital, days in hospital
Inflammatory markers	IL-6, pro-inflammatory biomarkers, NK-cell count, leukocyte counts, immune monitoring, cytokine response, inflammatory mediators, biomarkers associated with complement activation, CRP, fibrinogen, D-dimer, urea, ferritin, LDH
Oxygen support	Oxygen requirement, supplemental oxygen, return to room air (RTRA), oxygenation
Respiratory support	Ventilated, mechanical ventilation, ventilator-free days, respiratory function, respiratory improvement, extra-corporeal membrane-oxygenation (ECMO)
O2 saturation	Oxygen saturation, markers of tissue hypoxia
Days in intensive care unit	Days in intensive care unit, ICU-free days
Clinical improvement	SAPS II score, multi organ dysfunction score (MODS), disease severity score, clinical improvement meeting the discharge criteria, physician-reported clinical status, successful clinical outcome, clinical recovery, clinical status, clinical cure, Sepsis-related Organ Failure Assessment (SOFA) Score
Radiological change	Tayler's scale, radiological findings, Computed Tomography findings, lung opacities, ground class opacities, patchy opacities
Adverse Events	Adverse events, TESAEs, Serious adverse events, abnormal laboratory measurements (primarily regarding liver function, e.g., ALT, AST)
Decrease in symptoms	Symptoms, symptomatology
PaO2/FiO2	Oxygenation if referred to PaO2/FiO2
Inotropic support	Inotropic support, vasopressor usage
Laboratory values	Biochemical parameters, blood values, chemistry, clinical chemistry parameters, hemoglobin, and platelet count + complete blood count, coagulation + hematology parameters, ABT, ALT, AST, liver function
Vital signs	Vital signs
Transfusion reactions	Transfusion reactions
Acute care facility length of stay	Acute care facility length of stay
Time to unfavorable outcome	Time to unfavorable outcome
Treatment escalation	Treatment escalation

Category	Included terms
Duration of treatment	Duration of treatment
Morbidity	Morbidity
Veno-venous hemofiltration	Veno-venous hemofiltration
Left ventricular ejection fraction	Left ventricular ejection fraction

Detailed description of ten randomly selected expanded access publications

1. Locati LD, Piovesan A, Durante C, et al. Real-world efficacy and safety of lenvatinib: data from a compassionate use in the treatment of radioactive iodine-refractory differentiated thyroid cancer patients in Italy. *Eur J Cancer 2019;118:35–40.*
2. Laux LC, Bebin EM, Checketts D, et al. Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results. *Epilepsy Res 2019;154:13–20.*
3. Bonovas S, Piovani D. Compassionate Use of Remdesivir in Covid-19. *N. Engl. J. Med. 2020;382:e101.*
4. Huemer F, Melchardt T, Jansko B, et al. Durable remissions with venetoclax monotherapy in secondary AML refractory to hypomethylating agents and high expression of BCL-2 and/or BIM. *Eur J Haematol 2019;102:437–41.*
5. Flaherty L, Hamid O, Linette G, et al. A Single-Arm, Open-Label, Expanded Access Study of Vemurafenib in Patients With Metastatic Melanoma in the United States. *Cancer J 2014;20:18–24.*
6. Breuer S, Maimon O, Appelbaum L, et al. TL-118-anti-angiogenic treatment in pancreatic cancer: a case report. *Med Oncol 2013;30:585.*
7. Samuels BL, Chawla S, Patel S, et al. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. *Ann Oncol 2013;24:1703–9.*
8. Towner W, Lalezari J, Sension MG, et al. Efficacy, safety, and tolerability of etravirine with and without darunavir/ritonavir or raltegravir in treatment-experienced patients: analysis of the etravirine early access program in the United States. *J Acquir Immune Defic Syndr 2010;53:614–8.*
9. Chopra R, Eaton JD, Grassi A, et al. Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. *Br J Haematol 2008;111:1122–9.*
10. Takahashi T, Prensner JR, Robson CD, et al. Safety and efficacy of gamma-secretase inhibitor nirogacestat (PF-03084014) in desmoid tumor: Report of four pediatric/young adult cases. *Pediatr Blood Cancer 2020;67:e28636.*

Real-world efficacy and safety of lenvatinib: data from a compassionate use in the treatment of radioactive iodine-refractory differentiated thyroid cancer patients in Italy

Setup

From November 2014 to September 2016, the lenvatinib expanded access program was open for patients in Italy to provide access to lenvatinib prior to the commercialization of the drug in Italy. 16 Italian sites participated in retrospectively reviewing the data of these patients. The study was approved by local ethics committees and was funded by an unrestricted grant from the pharmaceutical company and sponsor Eisai.

Patients

The expanded access program was open to patients with radioactive iodine resistant differentiated thyroid cancer. 94 patients were enrolled and included in the analysis population. Patients had a median age of 60 years (range, 23-82). Sixty-four percent of the patients received a previous systemic treatment and fifteen percent had an ECOG performance status (PS) of 2.

Intervention

Patients received lenvatinib, a tyrosine kinase inhibitor. Lenvatinib was given at an initial dose of 24 mg /day for 64 patients, 20 mg/day for ten patients and 14 mg/ day for 11 patients. Five patients started at 10 mg/day or less. Dosing could be reduced upon physician discretion. Treatment with lenvatinib continued until disease progression, a lack of therapeutic effect, or manifestation of unacceptable side-effects).

Outcome

The response rate (RR), progression free survival (PFS), overall survival (OS) and toxicity data during a period of 36 months were retrospectively collected. Overall, median PFS was 10.8 months (95% confidence interval (CI) 7.7-12). The OS was 23.8 months (95% CI, 19.7-25.0). All 82 patients that were evaluable for toxicity presented at least one adverse event (AE), of which 21 patients experienced at least one AE of grade 3 or higher (22.3%). The most common AEs included fatigue (13.6%) and hypertension (11.6%).

Comparison with other data

When comparing the expanded access program with the pivotal trial named SELECT, the authors conclude that: *'This retrospective observational study confirms the efficacy of lenvatinib in RAI-refractory, progressive, unselected DTC patients in a real-world practice in Italy. Global results, however, are inferior to those reported in the SELECT trial, being ORR 36% versus 64% and median PFS 10.8 months versus 18 months.'* The authors explain the inferior expanded access program results by the

fact that the expanded access program population included patients with a worse performance status and more prior treatment lines: 15% of the patients in the expanded access program had ECOG PS 2 compared with 5% in the SELECT trial, and 64% of patients in the expanded access program had already received at least one systemic treatment versus 25.3% in the SELECT trial.

The authors compare their expanded access program also to other real-world experience from a French expanded access program and a Swiss named patient program. In Italian, French, and Swiss experiences, lenvatinib was started in more heavily pre-treated patients, with worse performance status and more advanced disease compared with patients in the pivotal trial. The authors conclude that: *Interestingly, general patients' characteristics and clinical outcomes were consistent to those reported in a real-life experience carried out in France.*

Conclusion

The authors conclude that: '*Lenvatinib is active and safe in unselected, RAI-refractory, progressive DTC patients in real-life setting. The activity of lenvatinib could be improved if the drug administration started in the early phase of RAI refractory disease.*'

No recommendations for future studies are given.

Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results.

Setup

In January 2014, an expanded access program was initiated to provide cannabidiol to patients with treatment-resistant epilepsy as recent findings from several phase III clinical trials showed that add-on cannabidiol was efficacious for seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. Twenty-five sites in the United States participated and data were prospectively collected both during hospital visits and using patient diaries. The article reports interim results. An institutional review board at each site approved the expanded access program protocols, and the expanded access program was funded by the sponsor, GW Research Ltd, together with the Epilepsy Foundation, the New York State Department of Health and the State of Alabama General Funds. The data collection from the sites was company-initiated and medical writing support was provided by the sponsor.

Patients

The expanded access program was open to patients with treatment-resistant epilepsy receiving stable doses of antiepileptic drugs for ⩾ 4 weeks before enrolment. Of 607 enrolled patients, 580 patients were included in the efficacy analysis population. Patients had a median age of 13.1 years (range, 0.4-62.1). Patients were on a median of three other antiepileptic drugs in addition to cannabidiol at enrolment.

Intervention

Patients received oral cannabidiol, a cannabinoid binding to cannabinoid receptors CB1 and CB2. Cannabidiol was administered at a gradually increasing dose starting at 2-10 mg/kg/day until tolerability limit or till a maximum dose of 25-50 mg/kg/day was reached. The median CBD dose was 25 mg/kg/day and the median treatment duration was 48 weeks.

Outcome

The primary endpoint compared the change from 28-day frequency seizure to baseline. In addition, Adverse Events were monitored.

At 12 weeks, add-on CBD reduced median monthly convulsive seizures by 51% and total seizures by 48% compared with baseline. The proportion of patients with ⩾50%, ⩾75%, and 100% reductions in convulsive seizures were 52%, 31%, and 11%, respectively. These reductions in convulsive seizures were similar through 96 weeks. The most common AEs were diarrhea (29%) and somnolence (22%) and 33% of the patients experienced serious AEs.

Comparison with other data

When comparing the expanded access program with clinical trials, the authors note that both safety and efficacy are in line with previously reported results*: 'Results from this ongoing expanded access program support previous observational and clinical trial data showing that add-on CBD may be an efficacious long-term treatment option for TRE.' 'AE rates were similar to those reported in the initial analysis of the expanded access program, as well as to those reported in randomized controlled trials.'*

Several limitations to the study are mentioned. Besides the fact that the expanded access program was not placebo-controlled – a limitation that applies to all expanded access programs – *'there was inter-site variability in reporting methods, and information such as the reasons for AED dose reductions was not captured. Although parents/caregivers reported only the specific seizures that were countable, some seizure types that can be difficult to count (eg, absence) were included in the total seizure frequency data. In some of the site protocols, enrolment was dependent on predetermined seizure frequency, which was known to possible participants; hence, baseline overreporting cannot be completely excluded in this prospective data collection.'*

Conclusion

The authors conclude that: *'The pooled data across the expanded access program provides initial insights on the long-term treatment effect of CBD that support the recent evidence from rigorous, double-blind, placebo-controlled trials showing meaningful reductions in seizure frequency for patients who received add-on CBD vs placebo'.*

No recommendations for future studies are given.

Compassionate Use of Remdesivir for Patients with Severe Covid-19

Setup

The expanded access program provided access to remdesivir to patients hospitalized with COVID-19 in the United States, Europe, Canada, and Japan. The report is based on prospectively collected data from patients that received remdesivir between January 2020 and May 2020. Regulatory and institutional review board or independent ethics committee approval was obtained before each patient was treated with remdesivir and the program was funded by the sponsor, Gilead Sciences. The research was initiated, coordinated, and conducted by Gilead Sciences, and the report was written by a medical writer employed by the company.

Patients

The expanded access program was open to patients hospitalized with Covid-19, who had a confirmed SARS-CoV-2 infection and who were receiving oxygen support or had an oxygen saturation of 94% or less while they were breathing ambient air. Of 61 patients that received ⩾ 1 dose of remdesivir, 53 patients were included in the analysis. Patients had a median age of 64 years (range, 23-82). Nineteen patients received non-invasive oxygen support (36%) and 34 patients received invasive ventilation at baseline (64%) of which 30 received mechanical ventilation (92%) and four extracorporeal membrane oxygenation (8%).

Intervention

Patients received remdesivir, a broad-spectrum antiviral. Forty of the 53 patients received a full 10-day course of remdesivir, consisting of 200 mg administered intravenously on day one, followed by 100 mg daily for the remaining nine days of treatment. Ten patients received five to nine days of treatment and three patients got fewer than five days of treatment.

Outcome

Data on oxygen-support requirements, hospital discharge, and adverse events were collected. In addition, the authors assessed the clinical improvement based on a 6-point ordinal scale.

During a median follow-up of 18 days, 36 of the 53 patients showed improvement (68%) in oxygen-support requirements, including 17 of the 30 patients (57%) who received mechanical ventilation and were now extubated. By the date of the most recent follow-up, 25 of 53 patients (47%) had been discharged and seven patients died (13%). By 28 days of follow-up, the cumulative incidence of clinical improvement, as defined by either a decrease of 2 points or more on the six-point ordinal scale or live discharge, was 84% (95% CI, 70 - 99).

Comparison with other data

When comparing the expanded access program with clinical trials, the authors conclude that:

- 'Although data from randomized, controlled trials will soon provide more informative evidence regarding the safety and efficacy of remdesivir for Covid-19, the outcomes observed in this CUP are the best currently available data.'
- 'By way of comparison with a controlled trial, case series, and cohort studies, the 13% mortality observed in this remdesivir compassionate-use cohort is noteworthy, considering the severity of disease in this patient population; however, the patients enrolled in this compassionate-treatment program are not directly comparable to those studied in these other reports. Difference occurs for example in receiving invasive ventilation, coexisting conditions, and age.'

Several limitations to the study are mentioned: *'Interpretation of the results of this study is limited by the small size of the cohort, the relatively short duration of follow-up, potential missing data owing to the nature of the program, the lack of information on eight of the patients initially treated, and the lack of a randomized control group.'*

Conclusion

The authors conclude that: *'(These data) suggest that remdesivir may have clinical benefit in patients with severe Covid-19.'*

The authors advise the conduct of prospective randomized controlled trials: *'Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy.'*

Durable remissions with venetoclax monotherapy in secondary AML refractory to hypomethylating agents and high expression of BCL-2 and/ or BIM

Setup

Between April 2017 and September 2018, patients with Secondary Acute Myeloid Leukemia (sAML) received venetoclax within a named patient program in Salzburg, Austria. Efficacy and safety data were retrospectively collected. There is no information available on funding or ethics approval. Patients signed an informed consent for the use of venetoclax and to allow for collection of personal data.

Patients

The expanded access program was open to patients with secondary acute myeloid leukemia, meaning that patients developed AML either from an antecedent hematological malignancy. Seven patients were treated and included in the analysis population. Patients had a median age of 74 years (range, 65-82). Four patients had prior myelodysplastic syndrome (MDS), two patient developed leukemic transformation based on chronic myeloproliferative neoplasms, and one patient suffered from antecedent chronic myelomonocytic leukemia.

Interventions

Patients received venetoclax, a B-cell leukemia/lymphoma-2 (BCL2) inhibitor. After a stepwise ramp-up of venetoclax dosing, all seven patients received venetoclax daily at a dose of 800 mg. In four patients there was no dose modification, two patients received an intermittent 200 mg dose, and one patient had a temporary interruption.

Outcome

Progression-free survival (PFS), overall survival (OS), mutation status, BLC-2/BIM expression and toxicity were evaluated.

Median OS from venetoclax initiation was 55 days (range, 15-549). One patient with antecedent MDS and one with antecedent myeloproliferative neoplasm achieved a complete remission with a PFS of 505 and 352 days, respectively. Another patient achieved complete peripheral blood blast clearing within nine days after start of venetoclax. High BCL-2 and/or BIM expression in myeloblasts was found in venetoclax responders and response was significantly associated with OS.

Comparison with other data

When comparing the expanded access program with clinical trials, the authors conclude that: *'Despite the limited number of patients included in this retrospective analysis, exceptionally long response durations were observed with venetoclax monotherapy in pretreated sAML in comparison to previous studies.'*

Conclusion

The authors conclude that: *'Venetoclax monotherapy is safe and is able to induce durable responses in elderly patients with secondary AML after treatment failure with HMA.' 'Responses were clinically apparent within 4-6 weeks, favoring a short trial of venetoclax in patients without standard options. High baseline BCL-2 and/or BIM expression may identify responders to venetoclax treatment.'*

The authors suggest the conduct of future studies: *'These findings should be validated in future clinical trials.'*

A Single-Arm, Open-Label, Expanded Access Study of Vemurafenib in Patients With Metastatic Melanoma in the United States.

Setup

The expanded access program provided access to vemurafenib in 29 sites in the United States and data was prospectively collected after each treatment cycle of 28 days. After each cycle, patients returned to the treatment center for clinical assessment and new supply of the drug. The protocol, informed consent form, and accompanying patient information materials were approved by the institutional review board at each participating site before study initiation.

Patients

The expanded access program was open to patients with unresectable BRAF-v600 mutated positive metastatic melanoma. Of the 374 enrolled patients, 371 received treatment and were included in the safety analysis population. Patients had a median age of 53.5 years (range, 17-87). 109 patients had previously treated brain metastases (29%) and 59 (16%) and 12 (3%) patients had an ECOG performance status (PS) of 2 and 3 respectively. Outcome assessments were available for 241/371 patients.

Interventions

Patients received oral vemurafenib, a kinase inhibitor, 960 mg twice daily in cycles of 28 treatment days. Treatment was continued until disease progression, study termination by the sponsor following FDA approval of vemurafenib, death, or development of an intolerable adverse event. 135 patients completed at least 12 weeks of vemurafenib treatment, and 316 patients were receiving the full dosage of vemurafenib at the time of their last administration. Overall, 62 patients missed at least one dose because of AEs, and 42 patients required dose reductions because of AEs.

Outcome

The primary outcomes were objective response rate (ORR) as assessed by the physician, and the rates of treatment-related adverse events. The ORR was 54% (median time to response, 1.9 months). For patients with an ECOG PS of 0 or 1 (n = 210) and 2 or 3 (n = 31), the ORRs were 55%, and 42%, respectively. At least one treatment-related grade 3 AE was reported by 76 patients (21%), and six patients (2%) reported at least one treatment-related grade 4 AE. The most common treatment-related AEs were rash of any kind (37%), arthralgia (35%), photosensitivity reaction (26%), and fatigue (20%).

Comparison with other data

When comparing the expanded access program with clinical phase II and III studies, the authors conclude that:

- *'The relatively liberal entry criteria for this expanded access study allowed treatment of 3 patient groups not eligible or available for previous vemurafenib trials: (1) patients with poor PS (ECOG PS 2 and 3), (2) patients with previously treated brain metastases, and (3) patients previously treated with ipilimumab.'*
- *'The efficacy of vemurafenib has been remarkably consistent in the major studies reported to date. In the phase II study (BRIM-2) in which patients with previously treated BRAFV600- mutant metastatic melanoma received vemurafenib, a confirmed ORR of 53% was reported.'*
- *'In the pivotal phase III (BRIM-3) study, the confirmed ORR with vemurafenib therapy was 48% in patients with previously untreated metastatic melanoma, compared with 5% for dacarbazine."*
- *'The documentation of a 42% ORR in patients with poor PS is arguably the most important clinical finding derived from this study. In the phases II and III trials of vemurafenib, such patients were excluded'*

Conclusion

The authors conclude that: *'Despite limitations due to the nonrandomized design and short treatment duration, the results of this expanded access study confirm the previously reported rapid and high tumor response rate achieved by vemurafenib in the treatment of metastatic BRAFV600 mutation–positive melanoma. In addition, this study provides new data suggesting the efficacy of vemurafenib in several groups of patients with metastatic melanoma not addressed in previous trials.'*

The authors do not provide specific suggestions for future studies.

TL-118-anti-angiogenic treatment in pancreatic cancer: a case report.

Setup

This case report describes the use of TL-118 anti-angiogenic treatment in combination with chemotherapy via compassionate use. Data were retrospectively collected. Comments on ethical approval, funding or informed consent are lacking in the report.

Patients

The expanded access program was open to a 75-year-old female diagnosed with pancreatic cancer. She was inoperable and a stent was inserted into the common bile duct (CBD) to drain the biliary tract. In July 2011, she was treated with palliative chemotherapy consisting of gemcitabine and TL-118 via compassionate use.

Interventions

The patient received gemcitabine (1,000 mg/m2 day 1, 8, 15, 28 days) and daily doses of TL-118, an anti-angiogenic combination of four drugs, cimetidine (antihistamine), metronomic cyclophosphamide (alkylating agent), diclofenac (nonsteroidal anti-inflammatory drug) and

Sulfasalazine, an (angiogenesis inhibitor) orally. There was a temporary interruption of five months due to treatment related adverse events.

Outcome

Progression free survival (PFS), tumor markers (CA19-9) and adverse events were evaluated.

After three months of gemcitabine and TL-118 treatment, tumor markers and tumor size decreased; after six and eight months the patient '*nearly reached complete remission*'. On January 2012, the treatment with TL-118 was put on hold due to side effects, which included weakness and vomiting, and the patient was treated with gemcitabine monotherapy until April 2012. Between April and June, the patient did not receive any treatment because of cholangitis and stent replacement. In May 2012, tumor markers went up, so gemcitabine treatment was reinitiated. As tumor markers were still raising, TL-118 treatment was introduced again in October 2012. A month after renewal of TL-118 treatment, there was clinical improvement and a *'drastic reduction'* of tumor marker CA 19-9 again (from 1000 to 345 μ/ml. 16 months post-diagnosis the patient is still receiving TL-18 and gemcitabine and continues to be stable.

Comparison with other data

When comparing the expanded access program with pre-clinical trials, the authors conclude that: The potential of TL-118 in combination with standard chemotherapy in the suppression of tumor growth was also demonstrated in a pre-clinical trial in an orthotropic pancreatic cancer model in mice (unpublished data), mice with metastatic colorectal cancer and a phase II study in metastatic prostate cancer. Moreover, a phase II clinical trial of TL-118 for pancreatic cancer patients that have not yet been treated with chemotherapy was initiated by the sponsor, Tiltan Pharma Ltd. According to ClinicalTrials.gov (NCT01509911), this trial was initiated in 2012 and is still ongoing. No updates have been posted since February 5, 2016.

Conclusion

The authors conclude that: *'This report describes a new approach in treating pancreatic cancer, enabling patients to obtain a longer progression-free survival using this new anti-angiogenic drug combination, added on standard chemotherapy.'*

Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study.

Setup

From the 4th of August 2005 onwards, an expanded access program was set up to provide access to trabectedin during the regulatory review period. For this report, data from this expanded access program were retrospectively collected up to the 1st of October 2010. Patients with STS following progression of disease after standard therapy were enrolled. Trabectedin was jointly developed by Janssen Research & Development, LLC and PharmaMar S.A. Janssen Research & Development and LLC both funded this study and provided the investigational product. Five of the ten authors have served as scientific advisors and consultants to PharmaMar and Janssen Research & Development and JL and AA are employees of Janssen Research & Development. This study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the protocol.

Patients

The expanded access program was open to patients with various types of advanced soft tissue sarcoma (STS) following progression of disease with standard therapy. Of 1895 enrolled patients, 1803 patients received at least one dose of trabectedin and were included in the analysis population. Patients had a median age of 54 years (range, 16-89).

Interventions

Patients received trabectedin, a tris tetrahydroisoquinoline alkaloid binding to DNA. By interacting with proteins of the DNA repair machinery, trabectedin disrupts the cell cycle and inhibits cell proliferation. Trabectedin was planned to be administered at an initial dose of 1.5 mg/m2 via a 24-hour intravenous infusion beginning on day 1. Two dose reductions were allowed in the case of toxicity and were based on the investigator's judgment. The median duration of trabectedin treatment on study was 70 days, representing a median of three treatment cycles; ≥6 cycles were given to 535 (30%) patients. The median trabectedin dose intensity administered was 1.3 mg/m2 per cycle (86% ideal planned dose). 539 patients experienced a dosing delay and/ or a dose reduction.

Outcome

The objective response rate, treatment duration, overall survival and safety were evaluated. 807 patients had an evaluable objective response data of which 343 patients reported a stable disease. The median treatment duration was 70 days and the overall survival of patients with

leiomyosarcomas patients was 16.2 months, whereas this was 8.4 months for patients with other histology's. These leiomyosarcomas patients also had a higher objective response rate (6.9% vs. 4.0%).

Comparison with other data

When comparing the expanded access program with previous reports on trabectedin, the authors conclude that*: 'Results of this expanded access program are consistent with previous reports of trabectedin, demonstrating disease control despite a low incidence of objective responses in advanced STS patients after failure of standard chemotherapy."(..) Also the safety profile observed in this study is similar to that observed throughout the development program of trabectedin*.' The authors also conclude that the higher OS and objective response rate in leiomyosarcomas and liposarcomas were consistent with those data reported in prior clinical trials.

Several limitations to the study are mentioned: *'Firsty, this was an open-label expanded access program and was not designed as a randomized study with a direct comparison to another agent. Another limitation of this study is that the findings may not reflect a general population in respect to race, since the majority of the population enrolled were White and were of relatively good performance status (median ECOG score = 1). Lastly, we did not capture information on progression-free survival, which would be of particular interest for this agent that is not associated with a high ORR, but often results in stable disease.'*

Conclusion

The authors conclude that: *'Results of this expanded access program are consistent with previous reports of trabectedin, demonstrating disease control despite a low incidence of objective responses in advanced STS patients after failure of standard chemotherapy'*. They further write that: *'In this expanded access population of incurable advanced STS, trabectedin therapy results in durable disease control rates of approximately 30%, along with higher-than-expected rates of overall survival despite low rates of objective response. These data further support the palliative benefits of trabectedin in patients with advanced STS after failure of standard therapies.'*

The authors do not provide specific suggestions for future studies.

Efficacy, safety, and tolerability of etravirine with and without darunavir/ritonavir or raltegravir in treatment-experienced patients: analysis of the etravirine early access program in the USA

Setup

From September 2006 onwards, the international etravirine expanded access program provided access to etravirine in the US. Data were prospectively collected till week 48 and the protocol, any amendments and patient consent forms were approved by Institutional Review Boards. The study was conducted in accordance with the Guidelines for Good Clinical Practice and the ethical principles of the Declaration of Helsinki and editorial support was funded by the sponsor, Tibotec Therapeutics.

Patients

The expanded access program was open to patients with a proven HIV-infection being relapsed/refractory to multiple conventional antiretroviral treatment options. Of 2969 screened patients for the expanded access program, 2578 patients were included in the analysis population. Patients had a median age of 47 years (range, 43-52).

Interventions

All patients received two 100 mg tablets of etravirine, a direct inhibitor of the reverse transcriptase enzyme of human immunodeficiency virus type 1 (HIV-1), twice daily. Etravirine treatment was continued until loss to follow-up, virologic failure, treatment-limiting toxicity, pregnancy, or until etravirine became commercially available.

Outcome

Plasma viral load and CD4+ count were evaluated, together with safety and tolerability of etravirine in combination with other ARVs. These outcomes were evaluated in several subgroups using different antiretroviral therapy combinations in addition to etravirine.

In total, 62.3% of the patients achieved a viral load of <75 copies per milliliter by week 48. These viral response rates were similar across subgroups. Median CD4+ count steadily rose from baseline to week 48, resulting in a median change from baseline of more than 100 cells per cubic millimeter. Results in the subgroups ranged from approximately 80 cells per cubic millimeter to 130 cells per cubic millimeter. In the overall population, the incidence of serious adverse events was 2.0%. The most common AEs leading to discontinuation were rash (1.2%), diarrhea (0.3%), nausea (0.2%), sepsis (0.2%), and vomiting (0.2%).

Comparison with other data

When comparing the expanded access program with safety data from other clinical trials, the authors conclude that: *'Safety data from this trial are aligned with prior Phase IIb/III clinical trials with no new or unexpected safety issues observed.'*

Limitations include: *'genotypic/phenotypic data for etravirine were not available at baseline at the time most subjects in this analysis were enrolled (i.e., sensitivity to etravirine was unknown), ARV selection was not randomized within subgroups, disease characteristics at baseline showed some variability across subgroups, the contribution of background ARVs to overall virologic and immunological improvements is unknown, laboratory assessments were non-centralized, and the safety data are limited as only SAEs and AEs leading to treatment discontinuation were recorded.'*

Conclusion

The authors conclude that: *'This study suggests that clinicians were able to use etravirine with newly available agents, such as darunavir/ritonavir, and expanded access program drugs, such as raltegravir, to successfully construct suppressive regimens for treatment-experienced patients with HIV-1.'* As etravirine was utilized in combination with other new (darunavir/ritonavir) or experimental (raltegravir) antiretrovirals in a significant proportion of patients, this undoubtedly contributed to the response rates seen as well.

Defibrotide for the Treatment of Hepatic Veno-Occlusive Disease: Final Results From the International Compassionate Use Program

Setup

The expanded access program was a multicenter, multinational program, including both group access programs as well as single-patient emergency requests. Data collection was not driven by a protocol, but physicians were asked to complete prospective structured data collection forms at baseline, and outcome (survival) data. Physicians were responsible for obtaining appropriate approval from ethics committee and obtaining patient consent. The program was conducted from December 1998 to March 2009. The study was funded by the sponsor, Jazz Pharmaceuticals, including support for medical writing and manuscript editing.

Patients

The expanded access program was open to patients with hepatic veno-occlusive disease (VOD) after receiving a hematopoietic stem cell transplant. VOD is also known as sinusoidal obstruction syndrome (SOS) and may typically present with multiorgan failure. In total, 1129 patients from 311 sites participated in the expanded access program. Forty-three percent of all patients were under 18 years of age. The analysis population comprised of all patients from which forms were voluntarily returned by physicians, N=710. Patients had a median age of 25 years (range, 0.2 – 70.0).

Intervention

Patients received defibrotide, an oligonucleotide. At the start of the expanded access program, patients were dosed 10 mg/kg/day, but as soon as data the phase II study became available, the dose was amended to 25 mg/kg/day. Treatment duration was freely determined by the treating physician, with a minimum recommended treatment duration of 14 days.

Outcome

Patients received defibrotide for a median of 15 days (range 1-119). Fifty-one percent of all patients experienced at least one serious adverse event. The primary efficacy outcome was 100-day survival status after date of stem cell transplant. The overall survival estimate in this expanded access program at 100-days was 54% (95% 50.2, 58.0).

Comparison/interpretation by the authors

Although patients may have been different from trial patients, as '*The study included a heterogeneous population of patients with VOD/SOS, in part because of the real-world nature of the program and in part of differences in inclusion criteria in different regions*', the authors note that '*The day +100 survival and safety profiles in this study are notably consistent with those reported in other defibrotide studies*', and in detail discuss similarities across outcomes even in identified subgroups.

Several limitations to the study are mentioned: *'There was no protocol for this program and all reporting of patient data and outcomes was voluntary, without on-site monitoring. As such, in some cases, outcome forms were either not returned or not fully completed for all patients, which may have resulted in under-reporting of AEs that did not lead to death. In addition, the relatively shorter recommended duration of treatment in this program, compared with more recent studies also may have influenced efficacy and safety outcomes.'*

Conclusion

The authors conclude that: *'For patients in the CUP (…) the survival rate (…) is consistent with prior studies of defibrotide. The overall profile of serious and fatal events in this large study population of more than 700 patients was consistent with what has been observed in other studies of defibrotide for the treatment of VOD/SOS and was consistent with the manageable toxicities seen with defibrotide use in this setting.'*

As defibrotide received marketing approval at the time of writing, the authors give no advice on future conduct of trials.

Safety and efficacy of gamma-secretase inhibitor nirogacestat (PF-03084014) in desmoid tumor: Report of four pediatric/young adult cases

Setup

This case series describes treatment with nirogacestat (PF-03084014) in desmoid tumor in four cases via compassionate use. Data were retrospectively collected. The drug was provided by SpringWorks Therapeutics. Comments on ethical approval, funding or informed consent are lacking in the manuscript.

Patients

Four pediatric patients, aged of 2.5, 4, 17, and 19 years old, were included in the expanded access program to treat desmoid tumors, a type of typically non-cancerous soft tissue tumor. Of these patients, three had previously undergone surgery and/or systemic therapy, while the fourth patient received nirogacestat as initial treatment. The choice of nirogacestat was based on its anticipated low toxicity profile, severe pain at the tumor sites due to prior treatment failure, and in the case of the 2.5-year-old patient, due to the unavailability of alternative systemic therapy options following progression of the tumor after eight lines of therapy.

Interventions

Patients received nirogacestat (PF-03084014), a selective gamma-secretase inhibitor at 90 mg/m2 twice a day. Treatment duration ranged from six to 18 months. One patient simultaneously received celecoxib.

Outcome

Tumor response, response duration and adverse events were reported. One patient continued to have complete remission for nine months at time of publication. Two patients achieved stable disease, with a tumor size reduction of 18% and 42% for 17 and nine months, respectively, and the fourth patient progressed after a partial response. Only one grade 2 adverse event (diarrhea) was reported.

Comparison with other data

The authors were unable to compare the observed efficacy and safety with other data on nirogacestat, since no other data from pediatric and young adult patients were available. Importantly, the authors were the first to administer the drug dissolved in water, which was necessary for administration to the youngest patient. However, the authors 'have not conducted bioavailability or pharmacokinetic studies of nirogacestat administered in this manner'. The authors therefore note that: 'it remains unknown whether dissolution in water adversely impacts

the efficacy of nirogacestat, and additional studies should be undertaken to establish the feasibility of this approach in other patients'.

The authors primarily note *the 'small number of patients', 'lack of controls' and therefore call for 'further investigation is needed to understand its efficacy and safety in pediatric patients'.*

Conclusion

Based on the observed responses, the authors conclude that *'nirogacestat is a promising option for treating pediatric patients with desmoid tumors'.*

CHAPTER 8

Data collection for the sake of data collection

Adapted from:

Response to Open Peer Commentary 'Making It Count: Extracting Real World Data from Compassionate Use and Expanded Access Programs'

Polak TB, van Rosmalen J, Uyl-De Groot CA.

Am J Bioeth. 2020 Nov;20(11):W4-W5.

We have so far examined various use cases of leveraging data from expanded access programs for regulatory, reimbursement, or scientific purposes. We caution, however, to see expanded access as a panacea to generate useful evidence. In fact, the intensified burden on patients and physicians to engage in expanded access research should carefully be weighted against the potential outcomes of said research. Rozenberg and Greenbaum had published an opinion piece in the American Journal of Bioethics highlighting the underutilization of expanded access data. While we agree that this could have negative long-term health consequences, it is of importance to note that some data already has been used as shown through our previous work, and that data collection comes with both benefits and drawbacks.

In their open peer commentary: 'Making It Count: Extracting Real World Data from Compassionate Use and Expanded Access Programs',[52] Rozenberg and Greenbaum (R&G) discuss important matters concerning the added value of extraction of real-world data from expanded access programs. R&G address practical concerns and provide recommendations for the collection, analysis, and interpretation of such data. However, we feel four points warrant further clarification.

First, extracting real-world data from expanded access programs is not as novel as R&G presumed. In our recent review of drug approvals that incorporated real-world data from expanded access programs, we identified 49 approvals relying on these data.[50] Remarkably, some approvals date back to the 1990s. Back then, they were simply called observational, epidemiological studies, or 'expanded access studies': far less fancy than 'real-world data', yet perhaps equally effective.

Second, the authors seem to underestimate the conflicting interest expanded access brings to clinical trial recruitment. Similarly alluding to SARS-CoV-2 as the authors do, the Mayo Clinic authors of the convalescent plasma expanded access program point out that '*Physicians, hospitals and patients have the choices of this program (red: the expanded access program) versus a RCT. It is clear that over 90,000 patients and over 10,000 physicians elected to participate in the pragmatic, real-world evidence study design*'.[89] Hence, the expanded access program was actually competing with ongoing clinical trials. Randomizing only a fraction of the patients that participated in the expanded access program would have yielded far more actionable insights – urgently needed in times of a pandemic.

Third, at first sight it seems natural to extract real-world data from expanded access programs. It might be more appropriate to ask the question why that data is not being collected. Indeed, other scholars have argued it is ethically imperative to collect data when patients are treated with investigational medicine.[11] Taking a closer look, data collection requires infrastructure, such as well-designed and validated databases, but also legislation that facilitates data collection. It is for example unclear in what regulatory light expanded access data collection, or subsequent

analysis of that data, should be seen. Even more provoking is the fact that some European Union member states simply do not allow data collection within compassionate use programs.[50]

Fourth, the authors state that one might avoid using (placebo) controls, i.e., 'putting a real patient at risk', by using statistical techniques. Advanced statistical techniques may attenuate biases in analyses of observational (expanded access) data. However, their results are not as robust as those of randomized controlled trials – and robust results are needed in times of crisis. Statistical methods applied to observational data cannot fully replace randomized controlled trials.[92] Furthermore, a majority of drugs still fail to demonstrate effect in randomized controlled trials, hence, patients might have been better off being randomized to a control group.

We support the authors in their call for regulatory guidance and alignment as it comes to the opportunity expanded access programs bring to collect real-world data. We should not fail to learn from expanded access data, but by failing to randomize patients in the first place, we might learn nothing at all.

EPILOGUE

In this part, we have established that the utilization of data procured from expanded access is not purely anecdotal. Regulators, reimbursement agencies, and healthcare researchers routinely employ the data from expanded access programs.

To see how the results of our first paper would have developed over time, we updated our paper on the regulatory the use of efficacy data by FDA/EMA on the 1st of May 2023, updating results throughout 2022 with the help of Jasmin Schelhaas. This can be seen in Figure 11.

It is imperative to note that these figures have yet to undergo peer-review and have been presented solely in academic conferences. Nevertheless, we would like to show the updated statistics to the reader. Regulatory websites may not always be up to date, and hence information on 2022 may only come available in 2023. This delay could explain slight inconsistencies compared with the earlier figure, and also requires caution interpreting the numbers from 2022.

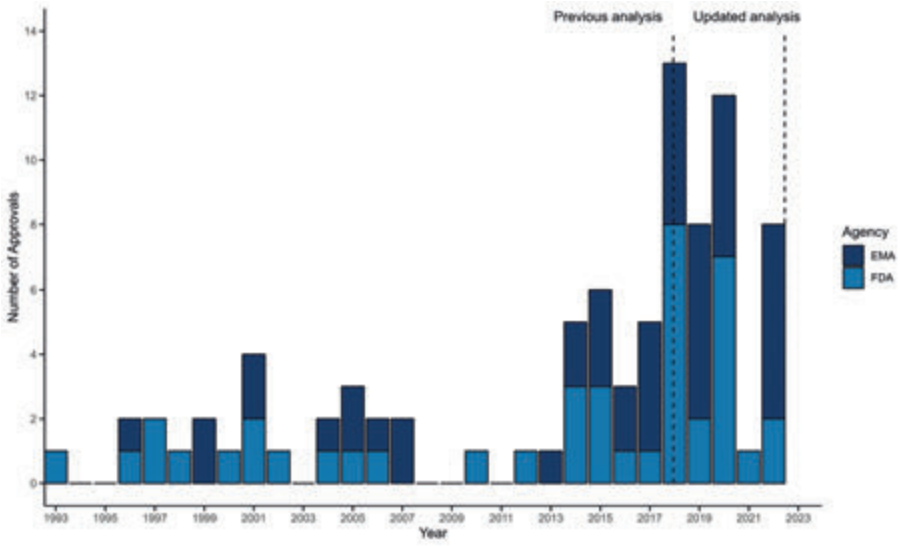


Figure 11: Updated Bar Chart analysis of EMA and FDA approvals that (partly) rely on data from expanded access programs to establish the profile of efficacy.

Our observations demonstrate that the previous trends have persisted, and regulators have increasingly been using expanded access data in decision-making. Despite the overwhelming enthusiasm surrounding this development, we caution against the mere collection of data without a clearly defined purpose, and a reliable tool to incorporate expanded access data into decision making. In the forthcoming chapter, we will develop such a statistical instrument specifically designed to accommodate the incorporation of expanded access data with data from randomized clinical trials.

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PART III

Statistical inclusion of expanded access data

PROLOGUE

Borrowing of historical data is a statistical practice that has gained prominence in recent years.[1–3] This approach involves the use of previously collected data for new research purposes, and it was originally proposed by Pocock in 1976.[4] Pocock's primary work was devoted to borrowing information from historical control groups of randomized trials, to potentially augment the current control group of a randomized trial. Pocock proposed strict criteria under which he deemed borrowing acceptable. Obviously, the type of control treatment should be the same. More stringently, information could only be borrowed when research was carried out in the same research centers, preferably by the same researchers. Patient characteristics should be similar, the method of treatment evaluation should be comparable, and there must be no external factors (unmeasured confounding) to believe that the results would differ. In practice, Pocock's criteria are almost never satisfied.[5]

The advantages and drawbacks of borrowing

In the ideal scenario, borrowing historical data offers several advantages. Firstly, it can save time and resources needed to conduct a trial. Rather than collecting data from scratch, researchers can use already existing datasets to answer current research questions. Secondly, borrowing data can be particularly useful when studying rare or difficult-to-find populations, where new data collection may be challenging or impossible.[6] Lastly, it could also help address issues with patient reluctance to be randomized to control groups, although we have witnessed in Part I that patients often benefit from being randomized to a control, rather than a treatment group. Apart from practical advantages, borrowing of information potentially leads to an increase in statistical power and precision by combining data from multiple studies or time periods.[2,7] But is all that glitters really gold?

There are several potential drawbacks to the use of borrowing information across data sets.[8] The primary concern is the introduction of bias and confounding.[9,10] Therefore, researchers must carefully evaluate the quality and comparability of historical datasets before attempting to integrate the data sets. This is the exact reason why Pocock invented his criteria.

The incorporation of (biased) datasets will undoubtedly increase the type I error, and without properly accounting for this introduced confounding, the chance of making erroneous decisions will inevitably increase.[11] For regulatory agencies, this is a critical concern, and it has so far decelerated the implementation of Bayesian borrowing methods in regulatory analyses. In recent years, such methods are now explicitly mentioned in the Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials by the FDA.[12] Practical borrowing examples exist where safety information obtained in adult populations is used to extrapolate safety to pediatric populations.[13] Nonetheless, methods of (dynamic) borrowing are not used at a large scale.

The types of borrowing

Various types of borrowing information exist. An excellent overview is provided by Viele et al.[2] Broadly speaking, there are two types of borrowing: static and dynamic. Static methods fix whether to borrow and to what degree. The easiest example of this is called pooling, and simply involves piling the two datasets together and analyzing if it were one large set.

Dynamic methods borrow depending on the similarity of the historical and current datasets. A simple approach is to first investigate the datasets to assess their similarity, and only combine the datasets if they are similar. This method is known as test-then-pool. First, the means of the two groups are tested through significance testing. If there is no significant change in group means, the groups are pooled, and else, the historical data is discarded. These methods perform dynamic borrowing, aiming to synthesize more evidence when data sources are 'comparable' and to synthesize less (or completely exclude evidence) as data sources differ increasingly. Primarily, these methods aim to address unmeasured confounding. The less similar data sets are, the less weight is addressed to the historical data. A variety of methods are developed in this field, such as the meta-analytic predictive prior,[14,15] the commensurate prior,[16,17] Bayesian hierarchical models and the power-prior.[7,15,18–20]

Hybrid borrowing methods

Recently, there have been innovations proposed by regulatory statisticians known as 'hybrid' methods,[14,21–24] that involve a two-stage procedure:

1. Attempt to account for measured confounding, for example through propensity score methods or covariate adjustment.
2. Attenuate residual unmeasured confounding through the use of dynamic borrowing methods.

This two-step procedure entails a dual safeguard by using two separate methods to measure the similarity of data sets on which subsequently the propensity and borrowing weights are based. Moreover, the analysis could be split between two independent statisticians, a principle known as an 'outcome-free' design[25]. Here, a first statistician independently models the propensity score process ignorant of the trial conduct and outcome. At trial completion, a second statistician analyzes the data using the allocation process predefined by the first statistician.

Borrowing from treatment groups through expanded access

As expanded access programs are the focus of our thesis, we explored whether we could extend the ideas of borrowing historical information from control groups into current control arms, to borrowing information from expanded access programs into current treatment arms. The following paper explores these ideas statistically, but Figure 1 provides the reader a graphical sketch.

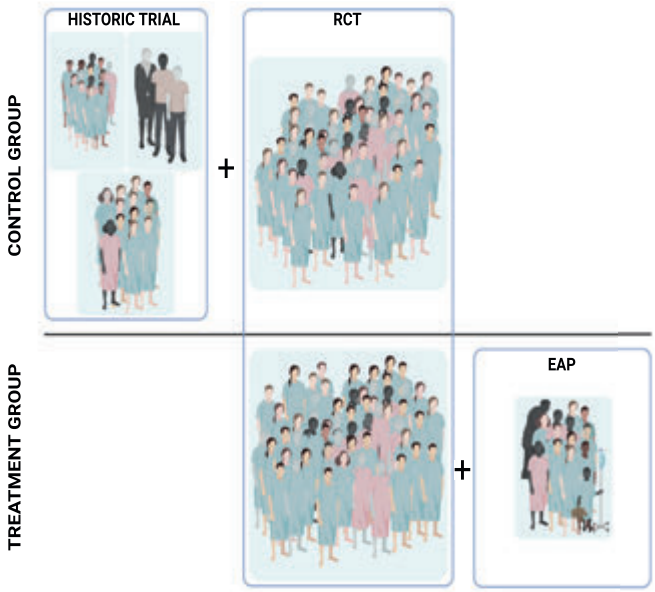


Figure 1: Graphical representation of augmenting current randomized clinical trial (RCT) control groups with historical control groups or augmenting current trial treatment groups with expanded access program (EAP) patients.

CHAPTER 9

Augmenting treatment arms with external data through propensity-score weighted power-priors: an application in expanded access

Polak TB, Labrecque JA, Uyl-de Groot CA, van Rosmalen J.
Under revision: Statistics in Medicine. Preprint arXiv:2306.01557, 2023.

ABSTRACT

The incorporation of 'real-world data' to supplement the analysis of trials and improve decision-making has spurred the development of statistical techniques to account for introduced confounding. Recently, 'hybrid' methods have been developed through which measured confounding is first attenuated via propensity scores and unmeasured confounding is addressed through (Bayesian) dynamic borrowing. Most efforts to date have focused on augmenting control arms with historical controls. Here we consider augmenting treatment arms through 'expanded access', which is a pathway of non-trial access to investigational medicine for patients with seriously debilitating or life-threatening illnesses. Motivated by a case study on expanded access, we developed a novel method (the ProPP) that provides a conceptually simple and easy-to-use combination of propensity score weighting and the modified power prior. Our weighting scheme is based on the estimation of the average treatment effect of the patients in the trial, with the constraint that external patients cannot receive higher weights than trial patients. The causal implications of the weighting scheme and propensity-score integrated approaches in general are discussed. In a simulation study our method compares favorably with existing (hybrid) borrowing methods in terms of precision and type I error rate. We illustrate our method by jointly analysing individual patient data from the trial and expanded access program for vemurafenib to treat metastatic melanoma. Our method provides a double safeguard against prior-data conflict and forms a straightforward addition to evidence synthesis methods of trial and real-world (expanded access) data.

INTRODUCTION

There is an increasing regulatory interest in synthesizing evidence from current (randomized) clinical trials with other data sources, to better understand the safety and efficacy of new drugs and medical devices.[1,26] Relevant data sources include historical control arms,[2,7] natural history studies,[3] single-arm trials,[22] and other sources of non-trial data, such as expanded access or compassionate use programs.[27,28] Ideally the incorporation of non-trial data increases power, reduces sample size, and helps to generalize results that are obtained in trial populations to more 'real-world' populations.[2] However, the combination of trial and external data introduces several sources of potential bias that need to be attenuated via modeling strategies.[7,11]

The variation in trial and external data can in general be attributed to either measured imbalances (e.g. in patient characteristics) between data sources and imbalances due to unmeasured confounding and other factors (e.g. center effects). Imbalances in measured characteristics can be addressed by a variety of methods such as covariate adjustment or propensity score methodology (e.g., stratification, matching or weighting). Propensity scores are frequently used to address biases that arise due to confounding in non-randomized experimental settings, by modeling allocation to treatment or control based on a set of covariates.[29] However, propensity scores may also be used to distinguish between trial and external data and can thus provide a solution to the issue of confounding in the synthesis of clinical trial data and real-world data.[23,30,31]

To address unmeasured confounding, statistical methods such as (hierarchical) meta-analytical models,[15,20,32] and the use of power-priors,[33–35] have been developed, both in frequentist and Bayesian settings. These methods perform 'dynamic borrowing', aiming to synthesize more evidence when data sources are 'comparable' and to synthesize less (or completely exclude evidence) as data sources differ increasingly. These synthesis methods were primarily developed to combine randomized controls with historical controls. In that context, Pocock suggested strict conditions relating to study design and patient characteristics to ensure that the historical data and the current trial are sufficiently comparable prior to performing a combined analysis.[4] One of Pocock's criteria is that the patient characteristics of the historical and randomized controls have a similar distributions, which may not be realistic in the context of non-trial, real-world data.[5]

Ample recent scholarship has been devoted to developing methods that simultaneously address both sources of bias. In these 'hybrid' approaches, propensity score methods are integrated into dynamic borrowing methods.[22,36] Multiply the number of standard propensity score methods (e.g. stratification, matching, weighting) with the number of available borrowing methods (such as the modified power prior, the meta-analytic predictive prior and the commensurate prior), and one may quickly get lost in the statistical jungle. In this paper, we aim to combine both fields of

research in an understandable manner, and we develop a conceptually simple and easy-to-use combination of the modified power-prior with propensity score weighting. In addition we give a detailed interpretation of the entirety of 'hybrid' approaches in the framework of causal estimands. Finally, we evaluate our methods through simulation and a case study by jointly analyzing the trial and expanded access program of vemurafenib in the treatment of metastatic melanoma.

The majority of aforementioned applications focus on the integration of external (historical) controls with current trial controls. Limited attention has been devoted to research on augmenting current treatment arms with external treatment arms. This lack of research may in part be attributed to the focus on trial design for regulatory product approval. After all, it may be difficult to find an external data set on active treatment usage before the product is readily on the market. Nonetheless, these data may be available through expanded access programs. In expanded access (also known as compassionate use or early access), patients who are ineligible for registered treatment options and ongoing trials may be granted access to active, unlicensed treatments prior to regulatory approval. Expanded access pathways have become increasingly popular in recent years, and data generated through expanded access form a substantial and increasing area of academic literature - especially due to the COVID-19 pandemic. Moreover, the analyses of such access programs have been integrated into regulatory and cost-effectiveness decision-making.[37,38] However, the statistical literature has not yet focused on models designed for the analysis of these types of programs and through this paper, we aim to make a first contribution to this area.

The remainder of this paper is organized as follows. Section 2 discusses the background of propensity scores, dynamic borrowing, and hybrid methods. Section 3 details our new proposed method. Section 4 evaluates our method with a simulation study, and Section 5 illustrates our method with a real-life expanded access program and trial. Finally, Section 6 concludes with a discussion.

Background of methodology

Notation

The data consist of a current (internal) trial y_0 and data from an external source y_e. In total, we have data on $N = N_0 + N_e$ patients. For every patient i, $i = 1, \ldots N$ in either the current study or the external source, we observe the outcome Y_i, a realization of Y_i, and the covariate vector x_i of length K, which is a realization of the set of covariates $\mathcal{X}$. Let Z be an indicator variable, where $z_i = 1$ if patient i belongs to the internal study and $z_i = 0$ if patient i belongs to the external data source. In our case study, the estimand is the baseline rate in a single-arm study and hence there is no treatment effect.

Propensity scores

Propensity scores are frequently used to address biases that arise due to confounding in nonrandomized experimental settings,[29] by modeling the allocation to treatment ($T = 1$) or control ($T = 0$) as a function of the covariates that one wishes to balance across these two groups:

$$e(x) = \Pr(\mathrm{T} = 1 \mid \mathcal{X} = \mathrm{x})$$

Equation 1

Among patients with the same propensity scores $e(x)$, covariates included in the propensity score will be balanced across the treated and untreated groups. Under the assumption that the variables in X are sufficient to make the treatment groups conditionally exchangeable ($Y^t \perp T | \mathcal{X}$), the propensity score can be used to estimate the causal effect of treatment. Weighting, matching, and stratification are the main methods in the propensity score toolbox.[39]

To use the propensity score to compare current trial data with external data, several authors have slightly redefined the propensity score.[21–23,36] Instead of modeling assignment to a control or treatment group, the propensity score is now used to model the allocation between current and external data (Z):

$$\lambda_i = \Pr(Z = 1 \mid \mathcal{X} = x_i)$$

Equation 2

where λ_i is the probability of patient i being in the internal study given the patient characteristics. Now, patients with similar propensity scores are equally likely to have been in the trial or external data conditional on $\mathcal{X}$. If the variables in $\mathcal{X}$ are sufficient to satisfy $Y^{t=0} \perp Z | T=0, \mathcal{X}=x$, then the internal and external populations are exchangeable.

The power prior

The power prior is one of the most prominent methods for dynamically borrowing information from the external data to aid inference of the current trial. The amount of borrowing - and hence the dynamic aspect - is based on how comparable the external data are to the current data. The more alike they are, the more is borrowed. An excellent review of these methods is provided by Viele and others.[2] The power prior is a Bayesian methodology that incorporates the external data into an informative prior to facilitate the analysis of the current study. In this informative prior the external data is downweighted by raising its likelihood to a power parameter δ, where the value of δ (with $0 \leqslant \delta \leqslant 1$) controls the amount of borrowing:

$$p(\theta \mid y, \delta) \propto \mathcal{L}(\theta|y_0)\mathcal{L}(\theta|y_e)^{\delta}\pi(\theta).$$

Equation 3

In the above specification, $\delta = 1$ results in a simple pooling of the two data sources, whereas $\delta = 0$ effectively ignores the external data. As it is unclear how δ should be chosen, Duan together with Ibrahim and Chen have proposed to estimate this in a fully Bayesian way,[34,35] in the so-called 'modified power prior' (MPP). This leads to:

$$p(\theta, \delta \mid y) \propto \mathcal{L}(\theta|y_0)\mathcal{L}(\theta|y_e)^{\delta}\frac{1}{C(\delta)}\pi(\delta)\pi(\theta),$$

Equation 4

Where integral of theta (θ) $C(\delta) = \int_{\emptyset} L(\theta|D_e)^{\delta}\pi(\theta)d\theta$ is a scaling constant to ensure Equation 4 abides by the likelihood principle. Reviews of different power-prior specifications and their characteristics can be found in Van Rosmalen et al. or Ibrahim and Chen.[7,40]

METHODS

Integrating propensity scores and power prior

Recently, various researchers have proposed 'propensity-score integrated hybrid approaches', which combine propensity score methodology with dynamic borrowing methods. Methods have been developed that focus on combining propensity score stratification with power priors,[21,22] or meta-analytic predictive priors.[14] Other methods focus on the inclusion of propensity score matching in dynamic borrowing.[23] Finally, a recent review of several of these methods has proposed both propensity score-weighting together with fixed and commensurate priors.[25] All these methods focus primarily on augmented control designs, designs in which the control arm of a trial is combined with external data on (historical) control arms.

The main rationale for all these methods is the dual safeguard mechanism within the two-stage analysis: observed confounding is addressed by using propensity score methods in the first stage, and remaining unobserved confounding is attenuated via dynamic borrowing methodology in the second stage.

We add to this literature by proposing a novel method based on propensity score weighting and the modified power-prior to augment the current treatment arm with external treatment data. The basis of our method, which we refer to as the ProPP, is the modified power prior, which is designed to only address imbalances due to unmeasured confounding (see Equation 4). To also safeguard against the effects of measured imbalances in patient characteristics, we apply propensity score weighting to this likelihood function before it is used in the MPP. The propensity-score weighted likelihood function is given by

$$\mathcal{L}(\theta \mid y)^{\delta} = \prod_i f(y_i \mid \theta)^{w_i}$$

Equation 5

where w_i, the weight used for patient i, is chosen as a function of the propensity score λ_i. If we now substitute this likelihood for the external data in Equation 5, we obtain:

$$\mathcal{L}(\theta \mid y_e)^{\delta} = \left(\prod_i f(y_i \mid \theta)^{w_i} \right)^{\delta}$$

Equation 6

Because our method combines propensity scores with dynamic borrowing based on the MPP, the effective weight for patient i is $\delta \times w_i$. In our approach neither δ nor w_i are allowed to take values greater than 1, so that the proposed method is always more conservative (i.e., provides additional protections against prior-data conflict) than the modified power prior. We additionally assess the causal and practical implications of the choice of weighting schemes.

Causal interpretations

The weights w_i can be chosen in a variety of ways. In applications of propensity score weighting for the estimation of treatment effects in observational studies, the weights are typically allowed to vary between patients within each group and depend on the estimand of interest. Before we choose w_i, we here want to provide an explicit causal interpretation of different modeling choices, or different choices of weights w_i (see Figure 2).

The value of *Y* can be different in $Z = 1$ and $Z = 0$ either due to random error or due to confounding (or selection bias) between *Z* and *Y*. An example of such a confounder would be any cause of the outcome that is not equally distributed in the internal and external data (e.g., C_1 in Figure 2). Dynamic borrowing methods based on differences in the outcome aim to balance the risk of pooling data with systematic differences (i.e., due to confounding) with the benefit of pooling data with differences only due to random error which increases precision. In this way, dynamic borrowing can never eliminate bias due to a variable such as C_1 but it can attenuate the bias by reducing the degree of pooling.

Ideally, differences in *Y* due to variables such as C_1 would be removed before dynamic borrowing determines the degree of pooling. Doing so would improve the bias and precision of our estimate. First, it would remove the bias due to C_1. Second, if C_1 increases the differences in *Y* across levels of *Z*, removing the effect of C_1 would reduce this difference and would therefore increase the degree of pooling while not sacrificing validity. The goal of the propensity score weights is precisely this: they re-weight the external data in such a way that the distribution of the variables used to compute the propensity score is the same across Z. In the re-weighted population there is no longer any relationship between the variables in the propensity score and Z. In Figure 2, weights constructed from the propensity score estimated using C_1 would in essence remove the edge between C_1 and Z. Of course, the propensity score-based weights only balance variables used to construct the propensity score. Any confounders which are not included in the propensity score will remain unbalanced across Z even in the re-weighted data set. As was the case before considering propensity score-based weighting, dynamic borrowing can balance the risk of unmeasured confounding with the benefit of increased precision, but with the additional benefit that some of the systematic difference in Y across levels of Z due to confounding has been removed through the propensity score-based weighting process.

Some caution is required when considering which variables to include in the propensity score model. Variables that are a cause of the outcome but unrelated to Z (C_2, Figure 2), are not necessary to include but they may help increase precision. Variables related to Z but not directly related to Y (C_3, Figure 2) should not be included and may in fact amplify any bias due to uncontrolled confounding between *Z* and *Y*.

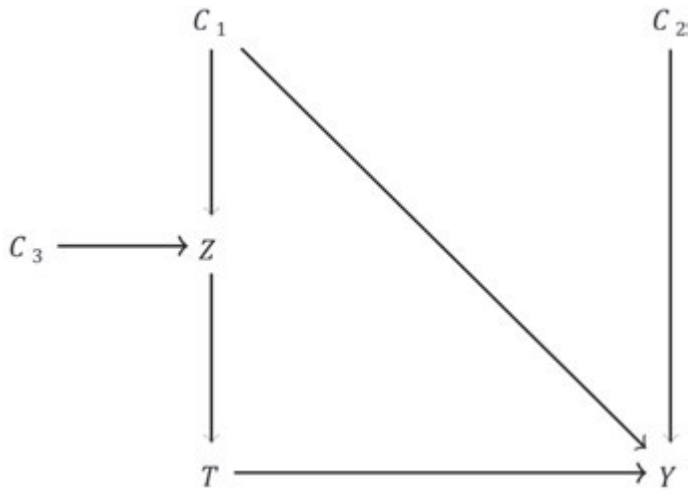


Figure 2: Directed acyclic graph to explore the causal implication of combining propensity scores and dynamic borrowing methods

The choice of weights

In dynamic borrowing, the usual goal is to improve the estimate of the outcomes from the trial. We should choose w_i according to a weighting scheme that corresponds with our estimand of interest, i.e., the average causal effect among those in the trial should be our target estimand (see Table 1). Therefore, we use a weighting scheme based that targets that estimand. However, we slightly adapt the above weighting scheme to make sure that no subject in the external data obtains a weight larger than 1. Weights larger than 1 would be undesirable for two reasons. First, this would amount to an inflation of the sample size in a Bayesian analysis, which in turn would lead to an overestimation in the precision of the estimates. Second, weighing a non-trial participant higher than current trial participants may cause regulatory concerns. Therefore, we propose to maximize the weight of the patients in the external data set at 1 (meaning that this patient is equally likely to have come from the trial). We set the weight w_i of all trial patients to 1, and of all external patients to:

$$w_i = \min\left(1, \frac{\lambda(x)}{1-\lambda(x)}\right).$$

Table 1: Propensity score weighting schemes under different populations of interest.

Trial	External	Population of interest
$\frac{1}{\lambda(x)}$	$\frac{1}{1-\lambda(x)}$	Average treatment effect
1	$\frac{\lambda(x)}{1-\lambda(x)}$	Average treatment effect of the trial
$\frac{1-\lambda(x)}{\lambda(x)}$	1	Average treatment effect of the external

Implementation for dichotomous outcomes

Here we illustrate the implementation of our method for data with a Bernoulli-distributed dichotomous outcome measure, with mean ∅ and likelihood function (before applying propensity score weights) given by $L(\theta)y_i) = \theta^{y_i} (1 = \emptyset)^{1-y_i}$. Filling in this expression in Equation 5gives the propensity score weighted likelihood function:

$$\mathcal{L}(\theta|y_i, w_i) = \theta^{\delta\sum w_i y_i}(1-\theta)^{\delta\sum w_i(1-y_i)}$$

Equation 7

Combining this propensity score weighted likelihood function with the posterior of the modified power prior in Equation 4 gives the joint posterior of the power parameter δ and the mean δ as

$$\mathcal{L}(\theta, \delta|Y, w_i) = \theta^{\delta\sum w_i y_i^e + \sum w_i y_i^0}(1-\theta)^{\delta\sum w_i(1-y_i^e) + \sum w_i(1-y_i^0)} \frac{1}{C(\delta)}\pi(\delta)\pi(\theta)$$

Equation 8

With a uniform *U*(0,1) prior for the mean parameter ∅ the integral in the scaling constant can be solved analytically as

$$C(\delta) = \int_\theta \mathcal{L}(\theta \mid y_e, w_i)^\delta \pi(\theta) d\theta = B\left(\delta\sum w_i y_i^e + 1, \delta\sum w_i(1-y_i^e) + 1\right)$$

Equation 9

If we further assume a *Beta*($\alpha_\delta \beta_\delta$) prior for δ, the joint posterior becomes

$$\pi(\theta, \delta \mid Y, w_i) = \frac{\theta^{\delta\sum w_i y_i^e + \sum w_i y_i^0 + \alpha_\delta}(1-\theta)^{\delta\sum w_i(1-y_i^e) + \sum w_i(1-y_i^0) + \beta_\delta}}{B(\delta\sum w_i y_i^e + 1, \delta\sum w_i(1-y_i^e) + 1)}$$

Equation 10

and after integrating out θ, the marginal posterior of δ is given by

$$\pi(\delta \mid Y, w_i) = \frac{B(\delta \sum w_i y_i^e + \sum w_i y_i^0 + \alpha_\delta, \delta \sum w_i (1 - y_i^e) + \sum w_i (1 - y_i^0) + \beta_\delta)}{B(\delta \sum w_i y_i^e + 1, \delta \sum w_i (1 - y_i^e) + 1)}$$

Equation 11

With the assumed prior distributions, the conditional posterior of ∅ given δ also has a closed-form expression, namely

$$\theta \mid \delta, Y, w_i \sim B\left(\delta \sum w_i y_i^e + \sum w_i y_i^0 + 1, (1-\theta)^{\delta \sum w_i (1-y_i^e) + \sum w_i (1-y_i^0)} + 1\right),$$

Equation 12

which greatly simplifies posterior sampling.

Algorithm

The sampling algorithm for the ProPP can be specified as follows:

1. Obtain the propensity scores as the fitted probabilities from a logistic regression for the allocation between current and external data, based on Equation 1.
2. Based on the population of interest and regulatory and statistical properties, choose a suitable weighting scheme from Table 1 to rescale the probabilities obtained in Step 1.
3. Draw a sample of δ from a uniform *U*(0,1) distribution and accept the values in that sample with probability given by Equation 11; other values in the sample are removed.
4. Draw a sample of ∅ from the conditional distribution in Equation 12, using the accepted values of δ from Step 3.

In Step 3, we use a sample of size 10,000, which should suffice because the rejection sampling method used in this step generates a random (independent) sample. This sampling algorithm is easy to program, and the code for the analyses in this paper can be downloaded from the GitHub of the first author.[14]

Simulation Study

Setup

We implement a simulation design to investigate the performance of our proposed method. The aim of this simulation study is to evaluate our proposed method and compare it with traditional

14 https://GitHub.com/TobiasPolak

approaches. Our simulation design was inspired by previous hybrid setups,[21,24] as well as motivated by the available setting of a (single-arm) clinical trial with external data from an expanded access program.

Data generation

We simulate the dichotomous outcome through the following data generating process:

$$\text{logit } y_i|x_i, z_i = \beta_0 + \beta x_i + \eta \times I(z_i = 1)$$

Equation 13

where β_0 is the intercept, β is a row vector of coefficients and η is a drift term. In our base case setting, we simulate data from N = 800 patients (N_0 = 400 in the trial, N_e = 400 in the external data), for $K = |X| = 5$ different continuous covariates X with $\beta_j = 0.1, j = 1,\ldots,5$. We set our base case intercept to $\beta_0 = 0$.

Several scenarios are explored to take into account that differences between trial and external outcomes can occur due to differences in covariates and/or a difference in the drift parameter. For the patient characteristics in the current trial, we assume normally distributed covariates with $X_0 \sim \mathcal{N}(\mu_0,\sigma_0^2)$.To account for possible differences in the covariate distribution in the external data, we assume that a proportion (ψ) of the patients in the external data have the same covariate distribution as the trial patients, and that the other external patients ($1 - \psi$) have data from a different normal distribution, with $X_0 \sim \mathcal{N}(0,1)$ and $X_e \sim (1 - \psi)\,\mathcal{N}(\mu_e,\sigma_0^2) + \psi\mathcal{N}(\mu_0,\sigma_e^2)$. We vary the value of ψ from 0.5 to 1 in the simulations, to assess the implications of our methods when covariates have different degrees of overlap.

To investigate the performance of our method, we consider the following four main scenarios:

1. Scenario 1: Drift. The change in outcome is only caused by drift η. We vary $\eta \in [-0.5,0.5]$. Both populations have the same covariate distribution, i.e. $X_0, X_e \sim \mathcal{N}(0,1)$, but these have no effect on the outcome distributions as $\beta = 0$.
2. Scenario 2: Mixture. The change in outcome is only caused ($\beta = 0.1$) by a difference in the underlying covariate distributions. The covariates come from a mixture distribution with $\psi = 0.5$. We assume $X_0 \sim \mathcal{N}(0,1)$ and $X_e \sim \mathcal{N}(\mu_e,1)$, where we vary $\mu_e \in [-0.5,0.5]$. There is no drift, $\eta = 0$.

Within these two scenarios, we also assess the following four settings:

1. Setting 1: Equal sample sizes. $N_0 = N_e = 400$
2. Setting 2: Larger external data. $N_0 = {}^1/_5 N_e = 400$
3. Setting 3: Larger current trial data. $N_0 = 2 \times N_e = 400$
4. Setting 4: Increase in the number of covariates, with 10 instead of 5 covariates

Additionally, we look at how sensitive our method is to (mis)-specification. Therefore, we also consider:

1. Scenario 3: No Mixture. The change in outcome is only caused by a difference in underlying covariate distributions. Unlike Scenario 2, there are no latent classes.
2. Scenario 4: Superfluous covariates. This setting mimics setting 1, but now some of the parameters β_j are forced to zero to simulate the inclusion of 'superfluous covariates' (i.e. C_3 in Figure 2).

Our parameter of primary interest is the baseline trial rate, β_0. Both in our simulation and in our expanded access use case, this is the response rate in a single-arm trial.

Methods and performance measure

The methods that we compare in our simulation study belong to the following three classes: 'naive methods' such as (i) Ignore: leaving out external data and (ii) Pooling: directly combining current trial and external data, 'dynamic borrowing methods' such as (iii) the modified power prior, and 'hybrid methods' such as (iv) the stratification + power-prior method suggested by Wang et al.[21,24] whilst borrowing at most 10% and 20% (of the current trial) of patients from the external data source. Our proposed method forms an addition to the hybrid methods. Performance will be assessed by measuring:

$$\text{RMSE} = E_{\beta_0}\left[\left(\beta_0 - \widehat{\beta_0}\right)^2\right]^{\frac{1}{2}}$$

Equation 14

and the type I error rate. To assess the type I error rate, we checked how frequently the objective response rate from the trial (through $\beta_0 = 0$) was within the equal-tailed 95% posterior credible interval of our estimand.

RESULTS

Scenario 1: Drift

In scenario 1 'Drift', patients from the trial are similar to patients from the external data (i.e., their covariates come from the same underlying distribution), but the outcomes differ due to a random drift term δ. The scenario of drift is the standard situation where methods such as the MPP are usually evaluated. The results for type I error rate and RMSE are shown in Figure 3 B. The RMSE of the analysis without external data (Ignore) is approximately 0.034. In case there is no drift, pooling the two data sources gives the lowest RMSE (approximately 0.023), 32% lower than ignoring the external data. The RMSE of pooling increases considerably when there is a nonzero drift, e.g., with a drift of $\delta = 0.375$, the RMSE of pooling is 0.05 - a 47% increase compared with ignoring external data, and the type I error rate becomes severely inflated.

For all cases except sub-setting 2, the RMSE and type I error rates of the ProPP and the MPP almost overlap and show the same characteristics (see Figure 3). In this scenario, where sample sizes are equal and patients are similar, all patients have approximately a probability of $\frac{1}{2}$ to be in the trial or the external data (and hence odds w_i of $0.5/(1 - 0.5) = 1$). When $w_i = 1$ for all patients, the ProPP specification in Equation 6 simplifies to the MPP specification in Equation 4. Sub-setting 2 ($N_0 = 400$, $N_e = 2000$) shows that a relatively larger sample size in the external data causes the 'Pooling' and the 'MPP' methods to exhibit an increased RMSE and an inflated type I error rate (up to 25 percent in the MPP). The weights w_i in the ProPP naturally account for such a difference in sample size and prevent this (unwanted) behavior.

Compared with the hybrid methods of Wang, our method has a lower RMSE, at the cost of an inflated type I error rate. Due to the pre-specified amount of borrowing, Wang's methods show a stricter control of the type I error rate in the simulations, but unlike the MPP and ProPP, this inflation continues to increase for higher values of drift, because the amount of borrowing is preset in these methods (see, for example, Wang 20 % in Figure 3A).

The results of this scenario show that the MPP and the ProPP have similar performance in terms of mitigating prior-data conflict due to unmeasured confounding. Note that the ProPP provides additional safeguards against measured confounding, which by design did not occur in this scenario. The fact that the amount of borrowed external data in the ProPP does not automatically increase with the sample size of the external data, in which this method differs from the MPP, seems an advantage. the hybrid methods proposed by Wang, the ProPP has lower RMSE, but this comes at the cost of a type I error rate inflation.

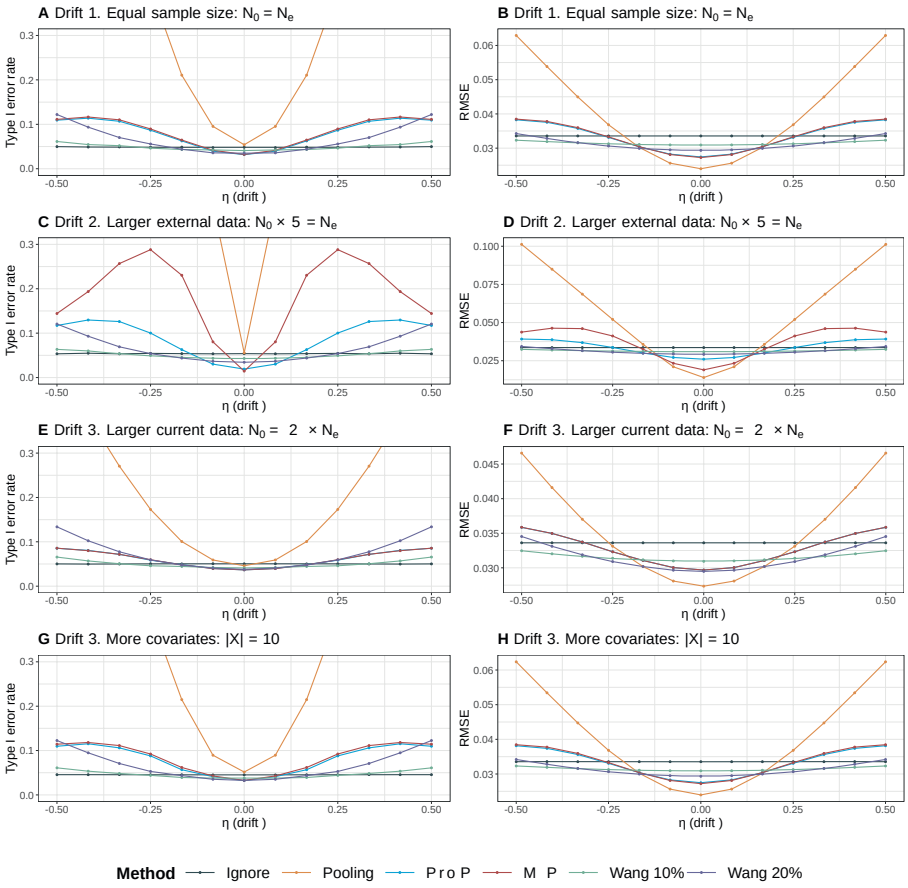


Figure 3: Comparison of different estimation methods in terms of type I error (left) and root mean squared error (RMSE) (right) when the difference in outcomes is in part driven by a random drift term. There is no difference in covariates (Setting 1).

Scenario 2: Mixture

In scenario 2 'Mixture', the differences in outcomes between the current data and external data are caused by a difference in covariate distributions between patient populations. For this situation, inclusion of covariates ought to improve the operating characteristics compared with excluding covariates (like in the MPP). Figure 4 presents the simulation results, and the RMSEs are depicted on the right-hand side. The RMSE of Ignore is a flat line at approximately 0.034 as there is no borrowing regardless of the outcome of the external data. Both Wang 10% (at 0.031) and Wang 20% (at 0.029) are also relative flat lines. Pooling reaches the lowest RMSE at 0.024 in non-zero drift, followed by the MPP and the ProPP at 0.0273 and 0.0274, respectively. Both the MPP and ProPP do show an increase in type I error rate, but remain more precise than Wang's methodology across our simulation range. By accounting for covariate effects using propensity score (i.e., rightly only incorporating similar patients), all hybrid methods yield a relatively stable and well-controlled type I error rate. This result is most clearly seen in Figure 3A, where both naive methods suffer from a large increase in type I error rate compared with the hybrid methods in Figure 4.

The results of this scenario show that the incorporation of covariates through propensity score methods provides an edge over the Pooling and MPP methods. The lower RMSE of these methods compared with ignoring external data is driven by the external patients that are similar to the current patients - and exactly these similar patients receive a higher weight. By including primarily similar patients, our estimate is improved. When there are more external patients to choose from (Setting 2), the chances of selecting the most similar patients increase, and the gain in precision becomes almost completely stable across settings. The increase in precision in Wang's method is driven purely by the prespecified amount of borrowing, whereas our method seems not to be impeded by borrowing limits, generally leading to a lower RMSE. Only in the unlikely setting of smaller external than current data, the ProPP relatively underperforms compared with Wangs methods - but still outperforms the MPP.

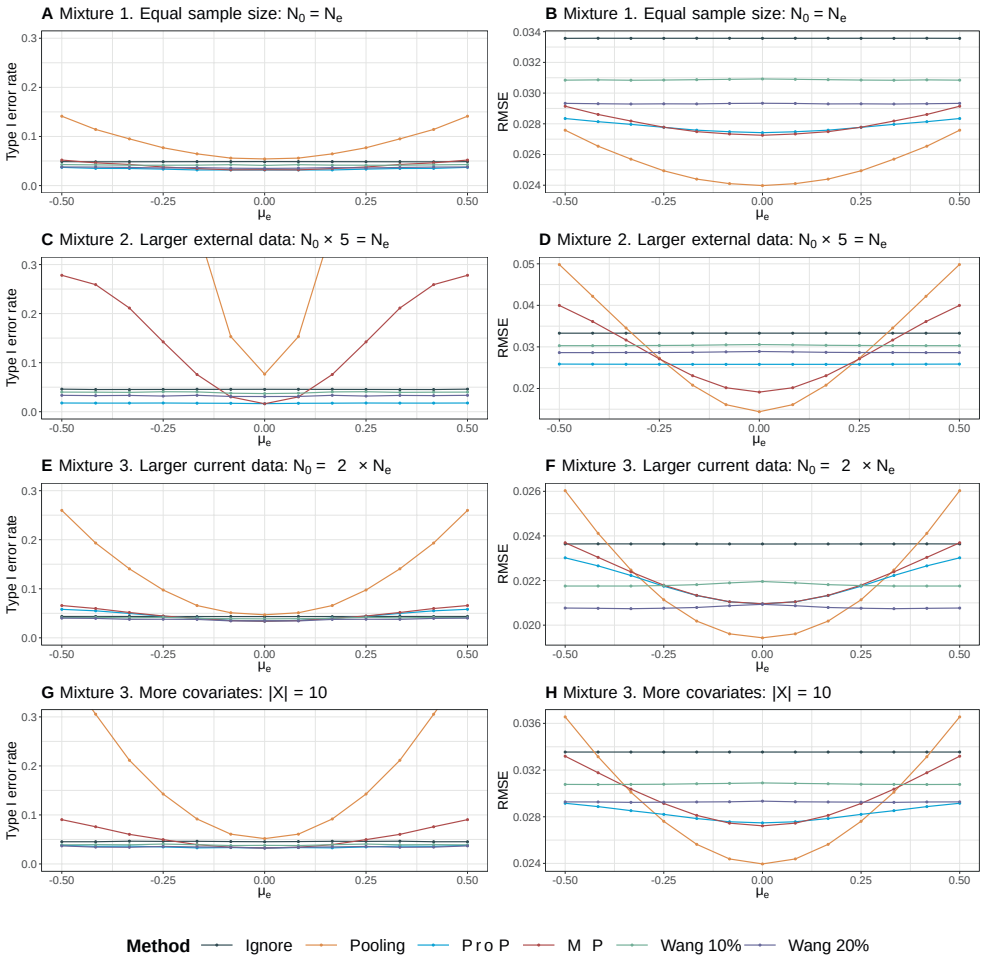


Figure 4: Comparison of different estimation methods in terms of type I error (left) and root mean squared error (RMSE) (right) when the difference in outcomes is in part driven by difference in covariates. There is a latent class structure in covariates. (Setting 2)

Sensitivity analysis: no mixture

We first explored how the methods would compare when there is no latent class structure in the distribution of the covariates, in the setting 'no mixture'. The results of this sensitivity analysis are depicted in Figure 5. Compared with the mixture setting (Setting 2), we observe a steeper increase in both RMSE and type I error rate due to the absence of the leveling effect caused by the latent class structure. Furthermore, the further the covariate distribution shifts, the less their overlap becomes. In case of a large difference in covariate distributions, the corresponding

decrease in the number of similar patients rendered the algorithm of Wang et al.[21] unable to complete the simulations in a considerable number of cases; at the extreme $\mu_e = -0.5$ these methods did not generate output in 65% of all simulations. We removed the line from the figures when the algorithm error rate exceeded 5%. This result highlights a small advantage of weighting-based schemes over stratification-based approaches. In the ProPP, the weights are simply set to 0 when external patients have very different covariate values than the patients in the trial, implicitly discarding part of the data but allowing the analysis to continue. The rest of Figure 5 shows increased RMSE and type I error inflation compared with Figure 4. The ProPP performs favorably compared with the MPP and Wang's suggested methods for a mild discrepancy e.g., $\mu_e \in (-0.25;025)$ between the covariate distributions. All in all, in the absence of latent classes, the ProPP (i) fares reasonably well for small differences between covariates and (ii) accounts for larger distortions when covariate distributions overlap decreasingly.

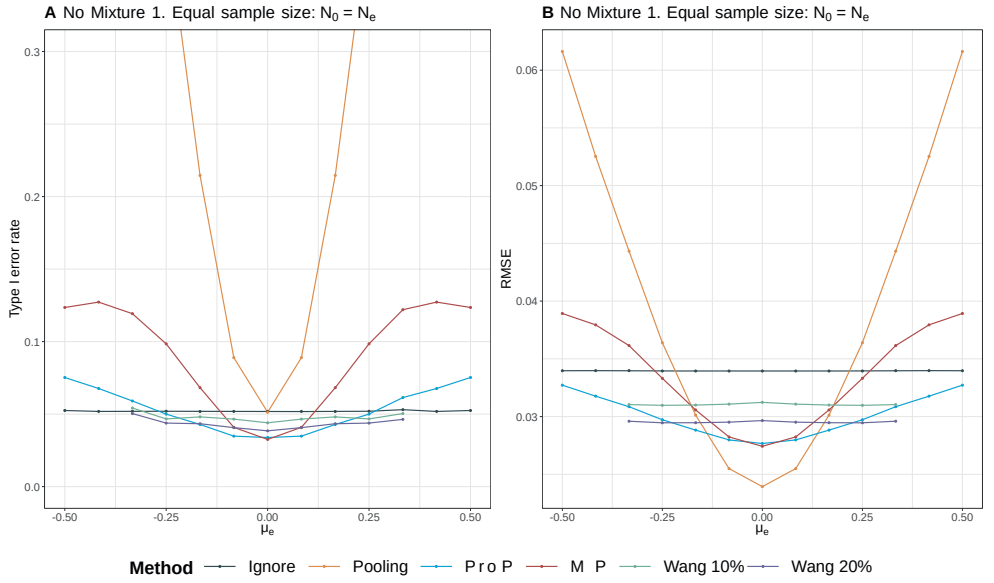


Figure 5: Comparison of different estimation methods in terms of type I error (left) and root mean squared error (RMSE) (right) when there is no latent class structure in covariates (Setting 3). Estimates have been removed if > 5% of the computations did not produces estimates.

Sensitivity analysis: superfluous covariates

In Supplementary Figure 1 in the Supplementary Material, we further examine the effect of including superfluous covariates, i.e. covariates that do not influence the outcome but do influence the allocation. We do this by setting $\beta_j = 0$, for $j = \{1\}, j = \{1,2\}, j = \{1,2,3\}, j = \{1,2,3,4\}$, whilst the overall effect of β remains constant ($\Sigma\beta_j = c$).

We observe that the RMSE is relatively similar or merely increases slightly along with the number of 'superfluous' covariates included in our model. Without superfluous covariates, the lowest RMSE of the ProPP is 0.02742 and attained when $\mu_E = 0$. The differences are almost negligible: when one covariate is superfluous, the RMSE increases to 0.02745 (0.1%) and when three covariates are redundant, the RMSE increases to 0.02758 (0.6%). The ProPP method seems to outperform the methods of Wang across the range of our simulation set-up when including redundant covariates, which suggests that the ProPP is relatively robust to misspecification.

ILLUSTRATION: EXPANDED ACCESS OF VEMURAFENIB FOR MELANOMA

To illustrate our method in practice, we here jointly analyze data from the vemurafenib clinical trial and the vemurafenib expanded access program. Vemurafenib is a drug currently approved for the treatment of late-stage melanoma harboring a V600E BRAF mutation. The United States (US) Food and Drug Administration (FDA) approved vemurafenib in 2011 for patients who progressed on chemotherapy based in part on a single-arm phase II study ($N = 132$).[41] The European Medicines Agency (EMA) approved vemurafenib in 2012.

In addition to the regulatory studies, expanded access programs were set-up to grant patients unable to partake in the trials the opportunity to access vemurafenib prior to regulatory approval.[42] At 29 sites across the US, 371 patients received vemurafenib while simultaneously generating data on the treatment patterns, safety, and efficacy of vemurafenib in a real-world setting. We obtained individual patient data from the trial and expanded access program through the data sharing platform Vivli. The data access request and analysis plan can be obtained online through Vivli.[15]

The inclusion criteria of the expanded access program were less stringent than the criteria of the clinical trial, recruiting a broader patient population compared with the trial. For example, patients could only be included in the trial if they had an Eastern Cooperative Oncology Group (ECOG) performance score - a measure of physical fitness - of 0 or 1, whereas in the expanded access program, 19% of the patients had a worse performance score of 2 or 3. Similarly, 75% of patients in the EAP had stage M1c disease, meaning the cancer had spread throughout the body, compared with only 61% of patients in the trial. Table 2 displays the differences in patient characteristics among a subset of (prognostic) variables across the trial and the expanded access program. For the expanded access program, 64% (241/371) of expanded access patients had efficacy assessments available and were included in the analysis.

15 https://vivli.org/combining-data-from-expanded-access-programs-and-conventional-clinical-trials-a-statisticalapplication-to-vemurafenib/

Table 2: Characteristics of the patients participating in the vemurafenib expanded access program (EAP) and trial.

	Clinical Program	
Characteristic	**EAP, N = 241[1]**	**TRIAL, N = 132[1]**
Age at enrolment	53 (13)	50 (15)
Gender assigned at birth Female		51 (39%)
Female	95 (39%)	51 (39%)
Male	146 (61%)	81 (61%)
Melanoma stage		
M1a	22 (9.1%)	33 (25%)
M1b	26 (11%)	18 (14%)
M1c	182 (76%)	80 (61%)
Unresectable Stage III	11 (4.6%)	0 (0%)
ECOG performance status		
Grade 0	112 (46%)	61 (46%)
Grade 1	98 (41%)	71 (54%)
Grade 2	30 (12%)	0 (0%)
Grade 3	1 (0.4%)	0 (0%)
Objective Response Rate	129 (54%)	75 (57%)

[1]Mean (SD); n (%)

Analysis and outcome

In the first stage of our analysis, we estimate the probability of patients being in the trial conditional on their baseline characteristics. Frail patients (with a ECOG score ⩾ 2) were not allowed to participate in the trial and we expect these patients not to be integrated in our analysis. The propensities are depicted in Figure 6. The 42 patients with weight 0 on the left-hand side are indeed all 31 patients with ECOG 2 and 3, as well as 11 additional patients with a baseline melanoma stage of 'Unresectable Stage III' the latter category was also not present in the trial.

The primary outcome of the trial and the expanded access program was the Objective Response Rate (ORR), defined uniformly as the fraction of patients with a complete response (CR) or partial response (PR). The estimate of ORR in the trial was 53% (95% confidence interval (CI): 44%-62%). In a Bayesian reanalysis, given a $U(0,1)$ prior for the ORR, the posterior is Beta(75+1, 132-75+1) distributed with posterior mean 56.7 % and 95% posterior credible interval (48.3%, 65.0%). The estimated ORR in the expanded access program was 54% (95% CI: 47%-60%), in a Bayesian reanalysis leading to a posterior that is Beta(129+1, 241129+1) with a mean of 53.5% and 95% posterior credible interval (47.2%, 59.7%). The analysis with the ProPP leads to a posterior mean of 56.4%, with a 95% posterior credible interval of (49.4%, 63.3%). The different methods are depicted in Figure 7.

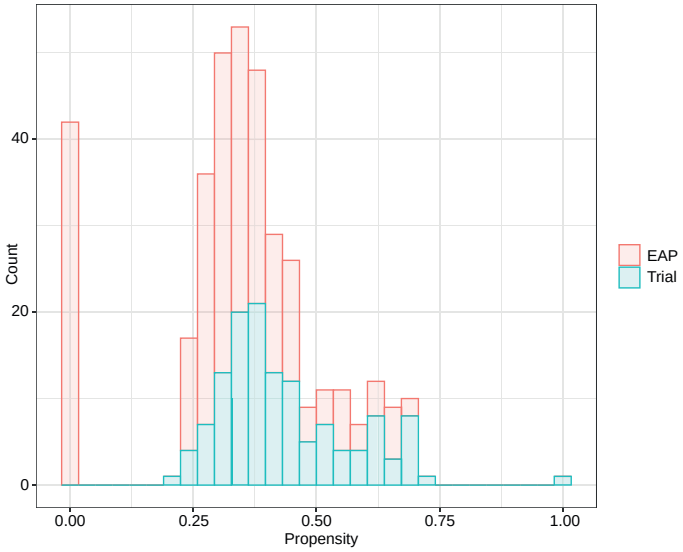


Figure 6: Distribution of propensity scores of patients in the vemurafenib trial and expanded access program (EAP).

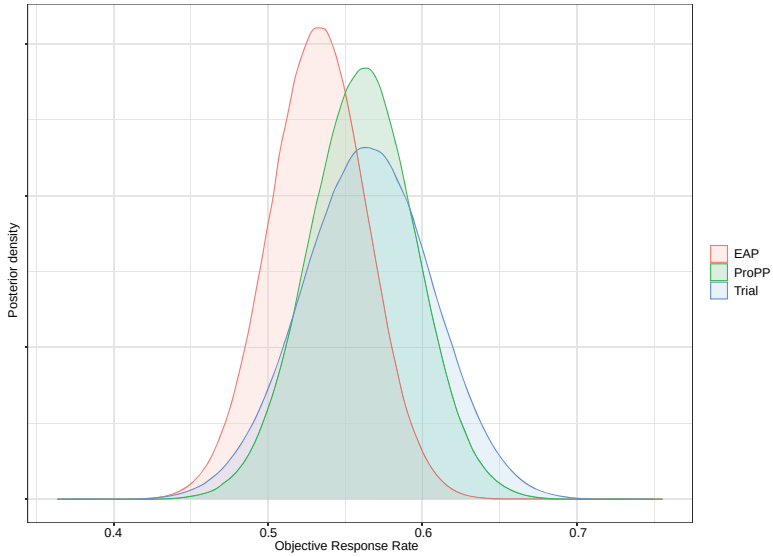


Figure 7: Posterior distributions of estimates of the Objective Response Rate computed using data from the trial only, expanded access program (EAP) only, or combined EAP and trial through the ProPP method.

We observe that the inclusion of expanded access data to augment the active trial arm leads to an increase in precision with a similar mean parameter estimate in this specific example of vemurafenib.

DISCUSSION

We developed a method to integrate the propensity score with variable power prior methodology. Our motivation stems from the increasing interest to incorporate external real-world evidence, and in particular expanded access data, into current trial data. Our novel ProPP method flexibly accounts for differences in outcomes and covariates between these two data sources in a two-stage design. Differences due to observed covariates are first incorporated through the propensity score. Remaining confounding is subsequently attenuated via the MPP in a dynamic borrowing setting. To our knowledge, we are the first to present the causal implications of the propensity score-integrated methods, and our modeling choices are guided by this causal interpretation. Our work explores the idea of augmenting treatment arms with current expanded access data. Overall, we observed that our method performs better than or on par with existing methods in a simulation study.

In simulation our method provides higher precision (lower RMSE) compared with both 'naive' methods and 'hybrid' methods, at the cost of light-to-moderate inflation of type I error rate. The additional two-stage safeguarding does not lead to a significant loss when there is no difference in outcomes due to underlying differences in covariates. This finding is in line with previous research exploring hybrid two-stage designs.[14,43] Additionally, our method can be shown to behave similarly to the standard MPP when covariates are equal across data sets and, unlike the MPP, naturally accounts for differences in sample sizes between data sets. Compared with previous methods,[21,24,36] our method needs no pre-elicitation of a fixed power parameter or a fixed amount of external patients to be borrowed, nor does it require decisions on trimming, distance measures, or the number of strata. On the other hand, it does entail a choice of prior specification. This degree of flexibility of the ProPP leads to an increase in precision, but it comes at the cost of lacking an 'outcome-free' design principle as the Bayesian estimation of the power prior takes into account the posterior probabilities, whereas fixed power prior weights do not. When contrasts in outcomes are in part caused by contrasts in covariates, all propensity score-integrated methods outperform 'naive' methods - a conclusion backed by a recent review.[25] Nonetheless, we echo prior scholarship that borrowing information entails a trade-off between cost (potential incremental errors in decision-making and type I error rate inflation) and benefits (increased precision, decrease in patient burden).[2,6,7] The high unmet need innate to expanded access programs together with the abundance of innovative statistical designs may tip the scale in favor of borrowing.

Our method, like all propensity score integrated designs, may be particularly applicable in a setting when a part of the external patients is similar to patients in the current trial. We argue

that expanded access programs harbor these characteristics as typically two types of patients are included. The first category are patients who are excluded from the trial due to their baseline condition, e.g., when they are too frail to participate in a trial, but are nonetheless granted access out of 'compassion'. For these patients, the inclusion/exclusion in the trial will probably be driven by a difference in expected outcomes. The second category consists of patients who would have been eligible for the trial but are 'unlucky', as a trial is already fully enrolled, or as trial sites are geographically out of reach. Although analyzing data of patients of the first category may lead to insights into the generalizability of treatments, it simultaneously may decrease the precision of the estimate and increase the chance of erroneous decision-making. Including the second category of 'unlucky', trial-like patients may on the other hand increase precision. Hence, an expanded access program may actually resemble the latent class simulation set-up, and we have shown that our method is able to correctly discriminate between these two classes of patients. Expanded access runs in parallel to ongoing trials, and these data hence form a 'current' external data source. This distinguishes expanded access data from 'historical' or 'non-current' external sources and limits the potential bias due to time trends. Furthermore, other scholars have suggested to explicitly incorporate the 'unmet medical need' or patient burden in trial design specifications - for example by adjusting the controlled type I error rate in diseases with extremely low survival rates (e.g., glioma). As expanded access by definition is only available for patients with a high unmet medical need,[44,45] this additional flexibility could be explored through the use of innovative statistical designs.

The similarity between data sources should play a decisive role in whether to integrate external and current data and if so, to what degree. The transparency in hybrid two-stage methods using propensity scores allows one to inspect the balance of covariates across data sets before proceeding with the analysis. As such, it provides a quantitative addition to the qualitative measures suggested by Pocock.[4] The availability of a causal interpretation of the estimates, combined with the additional safeguarding in hybrid methods, altogether provides a statistically rational argument to attempt to include expanded access patients into decision-making.

The acceptability of evidence synthesized from expanded access data in regulatory decision-making remains a topic of debate as these data are used in a qualitative, supportive manner.[27,37,46,47] Nonetheless, various regulators have put forth guidance on the (statistical) incorporation on 'real-world evidence'.[3,48] In addition to statistical arguments, there are also ethical considerations of incorporating expanded access data: ignoring expanded access data would imply treating patients with investigational medicine without reaping the benefits of additional insights on the safety and efficacy for future patients. Lastly, it denies participating patients the freedom to altruistically advance clinical research. One could therefore argue that more attention should be

devoted to the development of statistical methods to analyze expanded access programs. Our method provides a quantitative toolbox to augment treatment arms with expanded access data in a cautious and prudent way.

Limitations and future research

We acknowledge several limitations to our study. First, we have chosen a subset of the potentially available methods for integrating propensity score and dynamic borrowing, and we did not consider other relevant comparator methods such as direct covariate adjustment.[49]

Second, evaluating our method in terms of inflation of type I error rate could be questioned. For the true frequentist requiring strict type I error rate control, we know that given the external data, gains are typically not possible.[10] For the true Bayesian, operating characteristics such as type I error rate are less relevant. Furthermore, these methods are a combination of frequentist and Bayesian methodology, as the propensity scores are still estimated from a frequentist logistic regression model. A fully Bayesian design that integrates the estimation of the propensity score remains uncharted territory.[30,50] Our restriction of the propensity score weights is a result of this mixed methodology. It should be noted that our limiting of the weights to a maximum of 1, while possibly desirable from the point of view of a regulator, will result in weights that will potentially not be able to capture all of the confounding effects of the variables in the propensity score model.

Third, we derived the results from our method in the binomial setting. The binary outcome leads to a closed form posterior which greatly simplifies sampling and shortens computation time. We have not explored other outcome types, but it should be feasible to extend our method to time-to-event or normally distributed outcomes. Our method showed favorable computational performance compared with the method from Wang and others as described in their psrwe package,[21] where the propensity-score stratification sometimes failed to produce estimates.

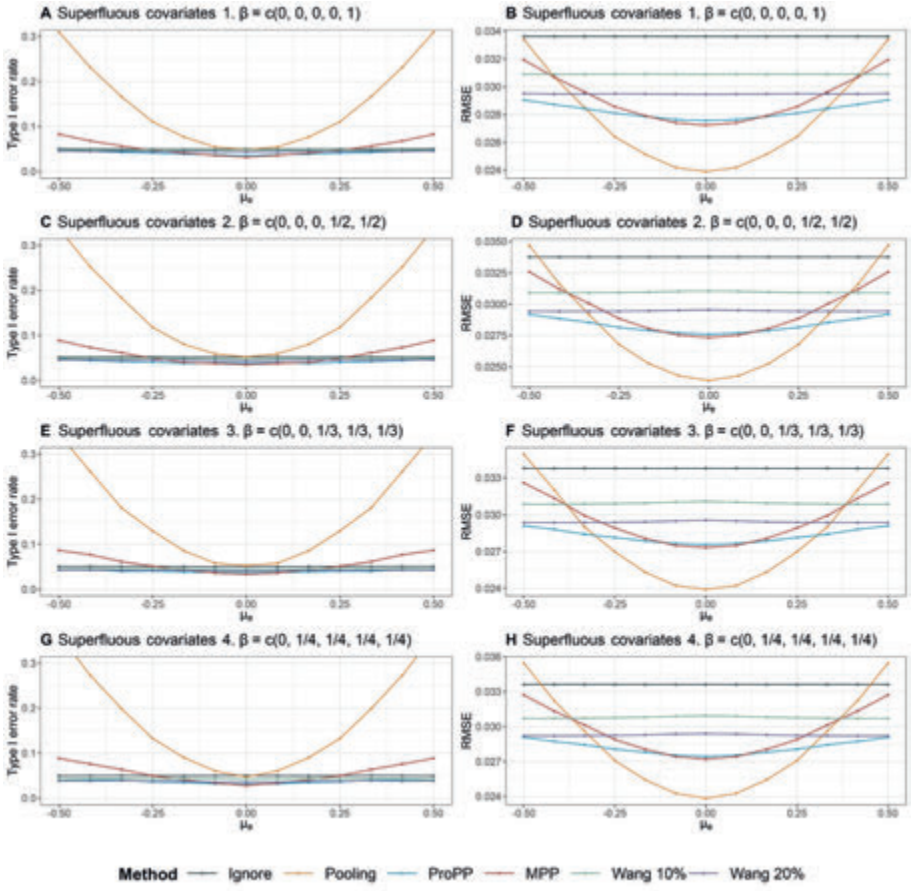
Finally, our simulation set-up including latent classes was inspired both by the original simulation set-up of Wang and others,[14,21,24] and by our analysis of patient populations in expanded access programs. The latent class setup may however favor hybrid methods in our simulation. The underlying assumptions and plausibility of such specifications should be tested prior to utilizing our suggested approach.

Conclusion

We developed a novel statistical design to augment the treatment arm of a current trial with external (expanded access) data. We illustrated our method through causal interpretation, simulation, and a real-life application to expanded access data. Our study shows that our

proposed method compares favorably with traditional and novel methods in simulation in terms of RMSE and type I error, and may be a useful addition to the growing field of propensity score integrated dynamic borrowing approaches. The potential decrease in trial size and associated patient burden, the high unmet medical need in expanded access programs, together with the precautionary statistical set-up may favor the inclusion of expanded access with current trial data. Nonetheless, the inclusion of evidence sources remains a trade-off between bias due to including non-trial data and increased precision due to increased sample size.

SUPPLEMENTARY MATERIAL



Supplementary Figure 1: Comparison of different estimation methods in terms of type I error (left) and root mean squared error (RMSE) (right) when the difference in outcomes is in part driven by difference in covariates. Some covariates do not influence the outcome ($\beta_j = 0$) and should have been excluded. This is a sensitivity analysis (Setting 4).

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PART IV

Policy implications and ethical considerations

PROLOGUE

Views on expanded access policy differ among jurisdictions. Where some countries lack well-defined pathways, others may have multiple established routes to access unapproved medicine. In the United States, the Food and Drug Administration simultaneously regulates market approval and expanded access for all states.[1] In the European Union, the European Medicines Agency approves products via a centralized procedure, but expanded access legislation is drafted on a national basis by individual member states.[2] This has led to a proliferation of national pathways.

In France, under certain conditions, medical companies can receive reimbursement for expanded access medicine, leading to a thriving market in unlicensed drugs.[3] In Belgium, pharmaceutical companies must pay a fee to initiate a program and subsequently provide the drug for free.[4] Regarding data collection, the United Kingdom offers integrative health technology assessment alongside expanded access through the Early Access to Medicines (EAMS) scheme,[5] whereas Austria specifically forbids the systematic collection of data through their (single-patient) expanded access pathway.[6] While Italy, Spain, and Belgium produce the largest number of publications per capita, Czechia, Slovakia, and Bulgaria have virtually no output on expanded access programs. The lack of harmonization in Europe has been subject of debate as the complexity of expanded access pathways increases.[7]

Policies and legislation regarding expanded access primarily have the same intent: providing treatment options to patients. However, the freedom to define expanded access per member state has led to a patchwork of national access pathways that vary in terms of regulatory requirements, procedures, and timelines, not to mention linguistic barriers. As such, these multitudes of polices may deter rather than expedite treatment options to patients in need. This lack of cohesion not only complicates matters for pharmaceutical companies, healthcare providers, and patients, but also hampers the generation of real-world evidence, which we have shown can be important for regulatory or reimbursement decisions, or in the dissemination of results developed through said programs. As a result, there is a growing need for compatible compassionate use legislation and European harmonization to balance access with evidence generation.

In this part, we will delve into concerns regarding the discrepancies in regulations, which may result in issues related to patient equity, and we will suggest policy enhancements to address these concerns. Subsequently, we will present a comprehensive analysis of the various viewpoints on expanded access as a data generation approach, with a particular focus on rare disease medicine, and explore potential strategies to integrate these different ideas. Lastly, we will evaluate expanded access as a means to conduct research from an ethical perspective.

Harmonization of expanded access pathways

We first will focus specifically on expanded access in the Netherlands, where two expanded access pathways exist already, as one can read in the Prelude.[8] Recently, a third non-legislated pathway was proposed and implemented. This pathway is named the 'DRUG Access Protocol' – which intends to unify data collection primarily for authorized, yet not reimbursed oncology medicine.[9] Although this is in various ways an innovative pathway, it further complicates the access routes in the Netherlands, which we discussed with the authors in the following article.

CHAPTER 10

The DRUG Access Protocol: access inequality and European harmonization

Polak TB, Cucchi DGJ, van Rosmalen J, Uyl-de Groot CA.
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We commend the initiators of the DRUG Access Protocol for their efforts to combine earlier access to medicine with structured data collection.[9] Although this is a novel program in the Netherlands, similar programs covering compassionate use, evidence generation, and reimbursement are already in effect in England (Early Access to Medicines Scheme) and in France (L'Accès Précoce).[10,11] The benefits of the DRUG Access Protocol in providing conditional reimbursement of registered drugs and thereby creating access are evident. However, the effects of the protocol in the setting of compassionate use (typically free of charge) requires further exploration.

First, the current set-up of access to compassionate use in Europe has led to a patchwork of national access pathways. The DRUG Access Protocol could further complicate the process of obtaining access to compassionate use, by introducing a novel national pathway specifically for oncology. Pharmaceutical companies without local presence or sufficient resources may prefer to provide access in countries with easier access pathways, which raises issues of equity in patient access. With the harmonization of clinical trials through the Clinical Trial Regulation and health technology assessments through the EUnetHTA initiative, we believe the need grows for compatible compassionate use legislation, rather than further diversifying pathways.

Second, the DRUG Access Protocol poses additional hurdles and workload to oncologists and companies as participation does not guarantee regulatory approval for compassionate use. Because this protocol is a voluntary, cooperative initiative and not a legally mandated pathway, regulatory approval still has to be obtained separately. This workload may deter rather than expedite access, especially for patients and oncologists in less specialized centers. The benefits of additional evidence generation may not outweigh the extra paperwork and research strains imposed on patients and physicians. In a broader context, the changing nature of compassionate use programs to provide 'research' rather than 'treatment' has been a growing source of concern among bioethicists.[12]

In recent years there has been an increased interest in compassionate use programs to generate evidence on safety and efficacy that supports trial results. The Compassionate Use Guidelines of the European Medicines Agency from 2007,[2] which do not mention the collection of efficacy data, seem out of date. We hope a guideline revision will clarify the value of compassionate use as real-world evidence, shed light on the concerns of equity to access raised above, stimulate harmonization of access pathways, and incorporate the experiences from the DRUG Access Protocol.

CHAPTER 11

Generating evidence from expanded access use of rare disease medicines: challenges and recommendations

Polak TB, Cucchi DGJ, van Rosmalen J, Uyl-de Groot CA, Darrow JJ.
Front Pharmacol. 2022 May 23;13:913567.

ABSTRACT

Patients with rare diseases often have limited or no options for approved treatments or participation in clinical trials. In such cases, expanded access (or 'compassionate use') provides a potential means of accessing unapproved investigational medicines. It is also possible to capture and analyze clinical data from such use, but doing so is controversial. In this perspective, we offer examples of evidence derived from expanded access programs for rare diseases to illustrate its potential value to the decision-making of regulators and payers in the European Union and the United States. We discuss ethical and regulatory aspects to the use of expanded access data, with a focus on rare disease medicines. The heterogeneous approach to expanded access among countries within the European Union leaves uncertainties to what extent data can be collected and analyzed. We recommend the issuance of new guidance on data collection during expanded access, harmonization of European pathways, and an update of existing European compassionate use guidance. We hereby aim to clarify the supportive role of expanded access in evidence generation. Harmonization across Europe of expanded access regulations could reduce manufacturer burdens, improve patient access, and yield better data. These changes would better balance the need to generate quality evidence with the desire for pre-approval access to investigational medicine.

INTRODUCTION

An estimated 7000 rare diseases affect approximately 10% of the population[1]. Although the number of patients with a given rare disease is by definition limited, the collective impact of these diseases is substantial. Yet only about 1 in 42 patients with a rare disease had even a single United States (US) Food and Drug Administration (FDA)-approved treatment option.[13] Before granting marketing authorization, regulatory agencies require evidence that the treatment benefits outweigh the risks, and generating such evidence requires time. Patients who have neither time nor approved treatments at their disposal and are unable to participate in trials, may seek access to investigational medicines via expanded access programs.[1]

Expanded access pathways allow patients with life-threatening or debilitating conditions to access unapproved medicines. Terminology for expanded access programs varies, as in English alone it is known as 'named-patient use', 'single-patient IND', 'compassionate use', or as 'expanded', 'managed', 'early' or 'special' access, all to denote non-trial access to unlicensed medicine.[14]

Historically, expanded access pathways were designed primarily to provide a treatment - to grant patients access to medicine outside of studies as last resort - although the collection of additional data was also contemplated.[15] Over the years, there has been a shift to increasingly emphasize the role of expanded access data. Although the primary intent of expanded access remains providing treatment to patients, data generated through expanded access have been reported in a large number of peer-reviewed publications, submitted in regulatory filings to the FDA and the European Medicines Agency (EMA), and used in health technology assessments.[11] However, opinions differ regarding to what extent data can be collected in the first place, and if so, how and when such data can be relied upon.

In this perspective, we clarify issues of data collection and subsequent analysis during expanded access programs in the US and European Union (EU). We first discuss detailed examples from the usage of expanded access data relating to rare disease medicines. Subsequently, we highlight the discrepancies in regulatory views on expanded access, discuss related issues of access inequality, and finally discuss ethical considerations of data collection and analysis. Lastly, we suggest means for improving expanded access data collection and use, with a particular focus on the EMA.

1 https://rarediseases.org/

REPORTING AND USE OF EXPANDED ACCESS DATA

Reporting of expanded access data in peer-reviewed publications

Expanded access has recently gained attention by the large number of compassionate use studies or case reports on treatments for SARS-CoV-2, such as remdesivir and convalescent plasma.[16,17] Unpublished data from our group indicate that from 2000 to 2022 over 1300 expanded access studies have been published. In oncology an estimated 198 expanded access studies were published with several examples concerning rare diseases from 2013 through 2020.[18] The median number of patients in publications that were not case reports (80%) was 153. This number ranged from N=7 in a publication reporting the experience of Austrian physicians using venetoclax to treat high-risk patients with acute myeloid leukemia refractory to standard therapy, to N=4,543 patients from over 50 countries in a report of the expanded access program for sunitinib to treat metastatic kidney cancer.[19,20] Both sunitinib[2] and venetoclax[3] received orphan designation for these diseases by the EMA.

Several drugs are associated with numerous publications flowing from expanded access, such as cabazitaxel, a chemotherapeutic for metastatic, castration-resistant prostate cancer.[21] It is associated with at least 10 expanded access studies, separately reporting experiences in Spain, Australia, Germany, South-Korea, Naples, Italy, the Netherlands, Canada, United Kingdom, and Europe.[22–31] The outcomes measured in these reports are heterogeneous, ranging from only safety data, to data on safety and quality-of-life, to data on safety and effectiveness, while others focus on prognostic modelling.[22,27,29,31] The heterogeneous reporting of different outcomes, and the multiplicity of reports across countries indicates the lack of harmonization or best practices in this setting.

Use of expanded access data in regulatory filings

Regulators require the conduct of clinical trials to determine safety and efficacy before granting marketing authorization. For rare diseases, performing such trials can be slow due to low patient enrolment, or even unfeasible or unethical.[32] Therefore, any evidence generated through expanded access patients should be harnessed to help clarify harms and benefits.

Through 2018 and starting in 1955 (FDA) or 1995 (EMA), 49 drug-indication pairs were approved by either the EMA or FDA based in part or in whole on expanded access data, 31 (63%) of which had an 'orphan designation' to support the development and evaluation of treatments for rare diseases.[33] This includes for example lutetium-177 oxodotreotide, a radioactive treatment for gastroenteropancreatic neuroendocrine tumors. Supplementary to the pivotal randomized

2 https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu305268
3 https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161617

controlled trial (N=229), data from 558 patients treated under compassionate use were considered in support of the indication. In the case of cholic acid, a treatment for patients suffering from various rare genetic disorders in bile acid metabolism, all evidence came from expanded access. The FDA and EMA evaluated data from 2 expanded access programs (N=63, N=22) to support the marketing authorization. The EMA approved cholic acid under exceptional circumstances, because

> *'the applicant was unable to provide comprehensive data on the efficacy and safety of the medicine under normal conditions of use. This can happen because the condition to be treated is rare or because collection of full information is not possible or is unethical.'*[4]

In the 39 cases where expanded access programs were included in the 'pivotal efficacy section' of regulatory submissions for rare disease medicines, 58% of all patients were treated under expanded access pathways.[33] Expanded access data can also be used to obtain special regulatory designations: in 2014, the FDA granted 'breakthrough designation' to uridine triacetate based on published case studies and expanded access data.[34] This highlights the role of expanded access in regulatory decision making in rare diseases.

Use of expanded access data in health technology assessments

As expanded access programs may provide the first source of evidence on the treatment use of investigational medicine in non-trial populations, various countries have explicitly combined expanded access with evidence generation or reimbursement schemes, such as l'Accès Précoce in France, the DRUG Access Protocol in the Netherlands and the Early Access to Medicines Scheme (EAMS) in the UK.[3,9,35,36]

In the United Kingdom (UK), drug approval is followed by a separate appraisal of cost-effectiveness compared to existing treatment options. Twenty-one percent of the health technology assessments conducted for the National Health Service in the last decade have relied in part on expanded access data.[11] We here highlight ipilimumab, a treatment for advanced, previously treated, unresectable skin cancer, which was approved in 2011 based on a trial involving 676 patients. For ipilimumab, the number of vials of drug needed is based on patient weight. As only 55 patients from the UK participated in the pivotal trial, the addition of expanded access patients helped the reimbursement agency obtain a better estimate of vial usage in the real-world patient population in their jurisdiction. At the reimbursement stage, data were pooled from 258 UK patients receiving ipilimumab through an expanded access program (using 1.19 vials of 50 mg on average) to supplement the data from the pivotal regulatory trial (using 1.51 vials of 50 mg on average). In this particular case, including data from expanded access led to a decrease in mean cost estimates.

4 https://www.ema.europa.eu/en/medicines/human/EPAR/orphacol

REGULATORY AND ETHICAL ASPECTS

The United States: treatment or research?

Despite the frequent use of evidence from expanded access programs, opinions differ on the extent to which data can be collected in this setting and in what way such data should be relied on. Expanded access pathways were first formalized by the US FDA in 1987.[1] The focus was primarily on providing treatment: in a meeting on January 14th, 1993, the National Institutes of Health discussed the 'research' status of patients in US compassionate use programs for gene therapies.[12] An FDA staff member noted that:

> *'The Office for Protection from Research Risk maintains that such patients cannot be considered research subjects. An investigator who receives a single patient compassionate use exemption cannot include the results of that patient data in any further reports of their research.'*

However, the current US legislation does not imply such a strict dichotomy between 'research' and 'treatment' – there even is no clarity to whether participants in expanded access programs should be considered patients or research subjects. In the US, the expanded access program occurs under an 'investigational new drug application' and the dispensing physician is considered an 'investigator'.[5] The main intent of expanded access programs — to provide treatment — is thus in tension with this regulatory framework, which generally views the purpose of an investigational new drug application to be the conduct of clinical trials, for which the primary intent is evidence generation. Over the years, expanded access has been increasingly viewed as an alternate means of collecting information on harms and benefits. In a 2020 conference, the FDA's principal deputy commissioner Janet Woodcock explicitly confirmed the agency's view:

> *'greater acceptance of data from (expanded access) treatment use to enhance generalizability in clinical development.'*[37]

Although the views stated above are 27 years apart, there still is no consensus among regulators, bio-ethicists and drug developers on the ability to collect and analyze data from compassionate use.[38–42]

The European Union's perspective

In the EU, individual member states regulate expanded access programs. Although the EMA governs marketing authorizations via a centralized procedure, the EMA has no formal authority over expanded access requests and plays only an advisory role. The regulatory reluctance to rely on data from expanded access programs stems from concern over data quality. In the Guideline on Compassionate Use of Medicinal Products from 2007, the EMA has dedicated a section titled

5 21 C.F.R. § 312.305

'*compassionate use versus clinical trials*' to address this issue:

> *'From a methodological point of view, clinical trials are practically the only means of obtaining reliable and interpretable efficacy and safety data for a medicinal product. Although safety data may be collected during compassionate use programmes, such programmes cannot replace clinical trials for investigational purposes. Compassionate use is not a substitute for properly conducted trials.'*[2]

But this section does not foreclose the use of expanded access data as a supplement to clinical trial data, rather than as a replacement for them. We are not aware of any evidence of companies or physicians bypassing trial guidelines and conducting expanded programs instead – some companies have refused expanded access requests to avoid jeopardizing trial enrollment.[6] Some worry, however, that allowing limited use of expanded access data could lead to increasing calls to broaden use of expanded access data. Illustratively, Belgian authorities describe a 'Frequently Asked Question', *'Could we apply for a Compassionate Use Program (CUP) or Medical Need Program (MNP) in place of an extension trial/open label study?'* Such concerns have led some countries to prohibit data collection through sponsors on expanded access studies. In earlier versions of this FAQ, the Belgian authorities responded that:

> *'no other data except pharmacovigilance data can be gathered which will only be used for the evaluation of the (..) program.'*[43]

This even precluded the use of safety data for purposes other than the evaluation of the expanded access program. In more recent versions, this has changed to:

> *'data collected (...) that are necessary for the conduct of the program (e.g. to check inclusion/exclusion criteria, to follow-up the B/R (benefit/risk) of a patient, pharmacovigilance data) could be used to enlarge the understanding of the treatment. It is not possible to collect more data than strictly needed for the conduct and evaluation of the program.'*[4]

Similarly, Austria prohibits data collection in a named-patient setting ('Heilversuch') stating that:

> *'named patient use is intended to facilitate the urgently needed treatment of a specific patient to avert a life-threatening or chronically debilitating situation. Systematic collection of data on safety and efficacy of the medicinal product used is not legally acceptable in this framework.'*[6]

Through our correspondence with regulators, we learned that Sweden does not allow data collection at all, and that Canada does not 'condone' data collection. Nevertheless, several publications on expanded access programs originate from Austria, Sweden, Belgium, and Canada.[44–51] These paradoxes demonstrate the unclear position of expanded access in evidence

6 https://www.fiercebiotech.com/biotech/biogen-holds-firm-denying-compassionate-use-for-experimental-als-drug

generation.

Access inequality

The current set-up of expanded access, in which individual EU member states retain full freedom to regulate these programs within their borders, forces companies to navigate a complex array of pathways that are often only accessible in local languages. Pharmaceutical companies without local presence or sufficient resources may prefer to provide access in countries with easier access pathways, raising issues of patient access equity.

The cost of expanded access creates further complications. Although manufacturers mainly provide treatment free-of-charge, France is willing to pay for treatment under expanded access, Italy has reimbursement options for expanded access in rare diseases, and the US allows the sponsor to recover the direct costs (e.g., manufacturing, shipment) from private or government payers. Most other countries prohibit paying for unlicensed medicine, or even charge the manufacturer for setting up an expanded access program. Belgium charges €19,835 to set-up a compassionate use program, and participation in the UK EAMS scheme comes at a fee[7] of £25,643.[52] These costs may discourage pharmaceutical companies from participating in expanded access programs, negatively impacting patient access.

Ethical implications

Providing treatment without collecting relevant data deprives future patients of the benefit of known outcomes and denies the patient the opportunity to altruistically contribute to generalizable knowledge. Prohibiting the use and collection of data could reduce manufacturers' willingness to provide expanded access, affecting even those countries that allow or encourage such reliance.

Furthermore, expanded access is non-randomized and unblinded, which can lead to confounding.[40,41] There are no guidelines on the quality assurance of data collection in expanded access – Good Clinical Practice is mandated by the EMA only for interventional trials.[53] Regulators or ethics committees should therefore ensure that expanded access does not undermine enrolment in traditional clinical trials adequate to generate high-quality evidence. The recent US convalescent plasma expanded access program for SARS-CoV-2 showed that this fear is not unfounded. Over 105,717 patients were enrolled in this program before trials where fully enrolled or completed.[54] Although a first analysis of these single-arm data hinted at beneficial treatment effects, randomized trials later did not confirm that convalescent plasma improved outcomes in inpatient care.[17,55]

7 https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams#fees

Lastly, it should be carefully determined whether the benefits of evidence generation outweigh the additional paperwork and research strains imposed on patients and physicians - the changing nature of compassionate use programs to contribute 'research' in addition to 'treatment' has posed concerns to bioethicists.[12] Ethical oversight could ensure that data collection respects the treatment intent of expanded access.

POLICY RECOMMENDATIONS

In this perspective we have illustrated the usage of expanded access data in rare disease medicines in scientific publications, regulatory filings, and health technology assessment. Although these data are frequently used, the role of expanded access in evidence generation, and the regulations governing data collection, are extremely divergent. The European setup of compassionate use is a patchwork of national access pathways, which may deter rather than expedite patient access to investigational medicine. We here offer several potential policy recommendations.

First, we call for regulatory guidance for data collection in expanded access settings, for example by including expanded access in real-world evidence frameworks, or offering means of integrating expanded access data in the guideline on patient registries.[56] This guidance should acknowledge the observational nature, suggest means for assuring data quality (remote monitoring, database requirements), and ensure that the burden placed on physicians and patients for data collection is justified by the needs for additional evidence generation. Lastly, it could highlight the types of data collection that may be most desirable, such as real-world patient demographics, dosing, or treatment adherence. For rare diseases, a more flexible approach regarding the use of expanded access data could be considered.

Second, the EMA guidelines could be revised to encourage the responsible use of expanded access data. Guidelines could clarify that expanded access data cannot replace clinical trial data, but may supplement such data to inform usage in non-trial populations or to increase patient numbers in rare disease. This is consistent with other efforts to expand use of 'real-world evidence', or evidence derived from non-trial data sources.[57] The lack of mention of efficacy data by the EMA is not in line with individual Member States' initiatives that explicitly combine expanded access and evidence generation. Such paradoxes should be prevented and a future revision of the guidelines should include efficacy outcomes.

The notion that clinical trials are the only means of obtaining reliable information does not align with the inclusion of expanded access data in decision making by the EMA: regulatory submissions have included data from expanded access programs to clarify the efficacy and safety profile of certain drugs.[33] The EMA guideline from 2007 discusses expanded access 'versus'

clinical trials, which is at odds with the recently stated vision of EMA executive director Emer Cooke who argued:

> *'We believe that the binary discussion between clinical trials and RWE is unhelpful as each approach brings its own strengths and weaknesses.'*[58]

The historical distinction between 'research' and 'treatment' intent is not always clear – nor should this imply that the primary intent (treatment) should prevent other (research) usages. Electronic health records are clearly intended to aid in the treatment of patients, but have been harnessed on a grand scale to simultaneously facilitate research.[59]

Third, the conduct of multinational observational studies warrants simplification. The European Clinical Trial Regulation expedites interventional studies via a shared assessment by member states. For non-interventional studies no such pathway exists, which hinders the set-up of studies. This potentially explains why publications frequently cover only the national experience within international compassionate use programs. The burden of setting up separate studies within each individual country or region affects rare diseases in particular, where the effort of initiating an observational study may not outweigh the limited data collection benefits. A centralized non-interventional study procedure could resolve these issues.

Fourth, we call for the creation of a unified EU expanded access pathway. The main goal of compassionate use is to provide 'early access' to investigational medicine for patients in need. The current set-up consists of a non-binding, optional advice procedure from the EMA, as well as 27 member states with multiple different pathways per member state. To provide expanded access, some countries require ethics committee approval, others do not. Some countries pay for treatment cost, others demand fees from manufacturers. Some countries allow liberal data collection, while others do not allow data collection at all. Harmonization and standardization of compassionate use pathways could reduce costs to regulators and manufacturers and resolve issues of equity in patient access, while also facilitating data collection to supplement trial data, which can be especially important for patients with rare diseases.

CHAPTER 12

The ethics of expanded access research

Polak TB, Fernandez Lynch H.
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With a variety of international analogues, expanded access allows patients to be treated with investigational medical interventions when approved options are inadequate and trial participation is unavailable.[1] Developed through AIDS patient advocacy, expanded access has always existed at the blurry intersection of clinical care and research. The pathway is governed by US Food and Drug Administration (FDA) research regulations for investigational new drugs and devices. Yet, unlike research, which aims to advance generalizable knowledge and offers only incidental benefit (if any) to study participants, the primary goal of expanded access, like all clinical care, is to benefit participating patients.

Recent trends have further blurred the lines around expanded access. There have been increasing global efforts to gather data from expanded access patients to support regulatory approval and coverage decisions, part of growing attention to real world evidence (RWE). Regulators have shown primary interest in expanded access safety data, but interest in efficacy data is also on the rise. From 1995-2018, the FDA accepted efficacy data from expanded access uses for 25 unique drug-indication combinations and the European Medicines Agency did so for 24, with frequency increasing in recent years;[33] further analysis shows these numbers have doubled. Meanwhile, the United Kingdom appraised data from expanded access programs in 20% of its coverage decisions in the decade from 2010-2020.[60] The FDA has also expressed greater acceptance of expanded access data to enhance generalizability in clinical development and sometimes suggests collecting expanded access data to support label expansions.[60] The FDA will occasionally grant approval based on efficacy data solely from an expanded access program, as it did, for example, with alpelisib's 2022 accelerated approval to treat overgrowth disorders.[61] In addition, patient advocates have successfully secured federal funding to support research use of EA data, specifically in the context of amyotrophic lateral sclerosis,[62] with the possibility of other disease areas to follow.

If companies, regulators, and payers are going to rely on – and sometimes solicit – these data, they must address a variety of ethical considerations relevant to the future of expanded access, including issues related to data quality, payment, transparency, and institutional review board (IRB) oversight, among others.

How useful is expanded access data?

There are several upsides to collecting data from expanded access patients. These data can provide insight regarding patient groups beyond those eligible for trials, such as those who are older, younger, or sicker. For rare diseases, it may not be possible to include every patient in a trial, but it is nonetheless important, given small numbers, to learn as much as possible from every patient. Given the provision of expanded access in real world settings, expanded access

data can provide information about factors like adherence that are harder to obtain in strictly controlled trials. Compared to other sources of RWE, such as claims databases or social media, EA is more structured, prospective, and reliable. In addition, when uncertainty remains about interventions that may help address a public health emergency like COVID-19, expanded access can facilitate access with greater data collection than alternative approaches such as emergency use authorization or early grants of traditional marketing approval. Finally, gathering data from expanded access patients allows them to altruistically contribute to scientific knowledge. These factors suggest ethical reasons to pursue expanded access data.[60]

However, there are also serious limitations, particularly when compared to traditional research. Most importantly, expanded access occurs in an unblinded, nonrandomized setting allowing only observational measures that may be rife with bias. Moreover, data collection is not governed by the same quality standards as clinical trials. Patient selection is an additional concern, as privilege likely influences which patients obtain expanded access (based on clinician knowledge and institutional support), replicating challenges seen across the health care system and limiting the ability of expanded access data to fill diversity gaps in clinical trials. These considerations make it ethically imperative not to overstate the value of expanded access data.

Who bears the burden and cost?

Although companies are allowed to charge the direct costs of drugs provided via expanded access, well-resourced companies usually provide unapproved drugs for free. The ability to collect meaningful data may incentivize smaller companies that might otherwise decline expanded access to also provide access, to the potential benefit of patients.

However, it is important to acknowledge that collecting expanded access data beyond minimum regulatory and clinically relevant requirements will be more resource-intensive for clinicians. Anecdotally, physicians already describe lack of compliance with regulations for submitting adverse events and summary reports for expanded access, let alone providing additional information to companies. Even at well-resourced institutions, clinicians may find this burdensome absent substantial additional support.[63] Although companies already incur costs in offering expanded access, to the extent data collection will benefit their regulatory and reimbursement prospects, they should financially support additional physician effort. Alternatively, since government payers also fund research and companies without any marketed products may be under-resourced, it may be appropriate to use grant funds to secure expanded access data in exceptional cases, especially rare diseases.[62]

From an ethical perspective, efforts are needed to balance the collection of meaningful expanded access data against burdens imposed on patients and physicians in clinical care, especially to mitigate the possibility of physicians choosing not to offer expanded access out of fear of unsustainable effort. Over time, technological advances, such as those supporting learning health systems, should help diminish the need for manual data entry. In fact, as pragmatic randomized trials rise in prominence, they will offer the ability to include more generalizable populations and real-world settings in research, reducing some of the need for expanded access while offering many of the benefits of expanded access data and addressing some of its drawbacks. However, compared to expanded access, pragmatic trials are more costly and time-intensive and, like other trials, will remain unavailable to some patients based on factors including location and timing. Thus, expanded access still has an important role to play – and potentially important data to offer.

What about transparency?

Given that expanded access is distinct from traditional research, it may fall outside current requirements to publicly report results, reducing transparency and the ability to learn from these data, while facilitating biased reporting of only positive outcomes. Although companies are required by law to post expanded access policies online and indicate whether expanded access is available when posting trials to ClinicalTrials.gov, expanded access use itself is not considered an applicable trial for registration or results reporting.[64] This makes sense in the context of clinical care, but when expanded access data are collected for research, research transparency requirements should apply. Posting expanded access research results will provide insight into whether and how expanded access benefits patients, information that is especially relevant to decisions about what resources should be devoted to this pathway. To address these concerns, FDA should issue guidance on reporting, data quality, and plans for enforcement, with broader clarity around the role of expanded access research within regulatory RWE frameworks, including when it is and is not appropriate.

What role for IRBs?

The role of IRBs will need to adjust as expanded access data are increasingly used for research. IRBs exist to protect research participants given conflicts that arise when their care is dictated by a research protocol rather than individualized clinical judgment. Expanded access has fit uneasily in this context, as clinical judgment is precisely what dictates treatment with an investigational agent outside a trial. Thus, IRBs reviewing expanded access (as required by regulation) historically have focused on confirming that potential individual benefits are likely to outweigh risks and that adequate consent is obtained. In fact, they may hesitate at the prospect of data collection that moves expanded access further from clinical care.

Yet IRBs must be careful not to unnecessarily inhibit expanded access data. They should not balk at requiring patients to agree to expanded access data collection as a condition of accessing an investigational drug, as this is no different than what is required of trial participants who may seek personal benefit from enrollment. Relatedly, IRBs reviewing plans for EA data collection may need to ensure that data are rigorously collected; other review bodies, such as scientific review committees, may also need to become involved to help maximize what can be learned from expanded access, as they often are in other types of research.

Conclusion

Expanded access does not fit squarely in the mold of either research or conventional clinical care. The value of expanded access data is limited compared with traditional trials, but it can provide a meaningful addition over other RWE sources, particularly for rare diseases. Companies seeking expanded access data should facilitate its collection, while FDA should mandate reporting and provide guidance to IRBs. Research goals for expanded access should not be overstated, nor should they supersede treatment goals at the heart of the expanded access pathway, but given current trends, ethical issues in expanded access data collection must be recognized and addressed.

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POSTLUDE

SUMMARY

Expanded access allows patients and physicians to access unapproved medical treatments. Established in 1987 during the AIDS crisis, this regulated pathway is only an option for patients who are unable to benefit from approved drugs or from trial participation. Over the years, the prominence of expanded access programs has grown, in part due to the increasing availability of online information on the development of new treatments, and, more recently, due to the search for treatments for COVID-19.

In my work, I participated in designing and implementing expanded access programs, with a particular emphasis on the efficient collection of data and the subsequent conversion into medical evidence. The motivation for the research in this thesis stems in part from the practical issues that I encountered in my day-to-day work. At first, I aspired to find a comprehensive overview on how to successfully implement expanded access programs with data collection based on research done by others – in the vain hope of repeating previous mistakes myself.

Soon, I discovered that there was no existing research on this topic. Although anecdotal examples were described in the literature, the use of expanded access to generate data and the various purposes for which these data could be used, such as regulatory decisions, publications, or reimbursement appraisals, were unclear. Moreover, expanded access programs were initially designed to provide treatment rather than conduct research. This potential shift in the nature of these programs could lead to unexplored ethical concerns, such as whether one should use these programs to generate data, under what circumstances, and when. Practical concerns also arose, such as the legality of collecting these data and the value of such data. My colleagues at work and mentors at Erasmus University and Erasmus Medical Center encouraged me to conduct this research independently. As the current work is the resulting collaboration, I will transition from using 'I' to 'we' from this point onward.

As befits writing a dissertation, our goal was to create a theoretical body of objective, reproducible research. But as theoretical findings have practical implications, we emphasized these throughout the thesis and discussed in depth two real-world examples of published expanded access programs to illustrate their practical applications in the opening pages of this book.

The main objective of this thesis is to ascertain the value of expanded access programs. In this regard, the notion of value is approached from different perspectives, including the clinical benefit derived by current patients and the merits of evidence generation for the benefit of future patients, while carefully considering the ethical and policy implications of viewing such programs as a partial means to generate information.

We have investigated the following research questions.

- ♣ What are the medical benefits for patients receiving expanded access to experimental treatments?
- ♦ What are the ways in which data obtained from expanded access programs are utilized, and by whom?
- ♥ Can existing statistical techniques be adapted to incorporate data from expanded access programs in the context of analyzing clinical trials?
- ♠ What ethical concerns emerge when using expanded access as a means to generate evidence, and how can improvements be made to expanded access policies?

The **prelude** contains a brief overview of the history of expanded access as a pathway to provide patients with access to experimental medical treatments, along with a detailed description – in Dutch - of the history and legislations of expanded access in the Netherlands. Additionally, we discussed the outcomes of two distinct real-world expanded access programs. In the first program, patients with treatment-resistant herpes viruses had the opportunity to access an investigational antiviral therapy, pritelivir. In the second program, patients with various diseases related to uncontrolled Epstein-Barr virus infections could access an unapproved cell therapy, tabelecleucel.

♣

In **Part I**, we studied how often 'promising' drugs advance through subsequent stages of research, as expanded access is often initiated based on presentations of preliminary findings. To limit the scope, we focused on the field of hematology. We assessed the clinical benefits of investigational drugs in acute myeloid leukemia using disease scales specifically developed to evaluate clinical merit of oncology and hematology drugs. Both oncology and hematology are associated with a high level of unmet medical need, and as such, they attract a considerable number of expanded access requests. Additionally, we used a universal metric of added benefit which allows to compare

benefits across disease areas, expanding beyond hematology and oncology. The Quality-Adjusted Life Year, or QALY, is a metric frequently used in cost-effectiveness research to study the added benefits of pharmaceuticals that are under evaluation for reimbursement in the United Kingdom.

We concluded that the average clinical merit of novel drugs in development is modest at best. From these results, it may appear that the likelihood of deriving substantial clinical gains from expanded access programs is limited. However, the practical reality may be more positive, as physicians and patients may be more inclined to participate in expanded access programs, and companies are more willing to initiate said programs for more effective drugs than for the average drug, resulting in a higher chance of deriving a clinically positive outcome for current patients. Indeed, we will see this line of reasoning confirmed in Part II. Additionally, and of particular interest in this thesis, there may be benefits reaped through the analysis of data of current expanded access patients to inform the clinical practice of future patients.

Knowledge generation through expanded access programs formed the basis of our subsequent research. When we started to write this thesis, information on the use of evidence from expanded access programs was predominantly anecdotal. Mandatory pharmacovigilance surveilled the occurrence of safety events in expanded access programs, some of which eventually informed drug labelling. The use of efficacy outcomes was undocumented – impossible or even considered unethical to some.

We created algorithms to enable the systematic analysis of a large volume of health policy documents, at times employing advanced techniques like optical character recognition to convert historic images into textual data. These automated approaches enabled us to search through vast bodies of documents available online from regulators such as the US FDA, the EU EMA, and cost-effectiveness research institutes such as NICE in the UK. We provided the first systematic overviews of the use of expanded access data in **Part II**. To make these results accessible to the general public, we created online research explainer videos and animations to accompany our publicly available code[1].

We discovered that the use of data from expanded access programs has increased over time, not only by regulators, but expanding to reimbursement bodies and researchers. Data collection is no longer limited to safety parameters, but has expanded to encompass efficacy outcomes, patient-reported outcomes, and even healthcare cost. It is evident that the utilization of expanded access has evolved past the realm of anecdote, to assume a substantive, and possibly even systematic

1 https://github.com/TobiasPolak

role in generating reliable evidence. With this in mind, we shift our focus to the practical aspect of statistically integrating these data with regulatory trial information.

♥

Expanded access programs may complement evidence obtained through regulatory trials, but both are frequently analyzed separately. In **Part III**, we developed a novel statistical technique to incorporate evidence from both data sources simultaneously. By combining Bayesian dynamic borrowing methods with propensity score matching techniques, we attempted to attenuate unmeasured and measured confounding. In a similar fashion to how researchers have aimed to incorporate information on historical control groups into the current trial control arm, we showed that it is possible to incorporate information from current expanded access treatment groups into the current trial treatment arm. We illustrated our method by acquiring and analyzing individual patient-level data of participants in the trial and expanded access program of vemurafenib, a treatment for breast cancer.

Where the interpretation of expanded access data had so far been qualitative, now a quantitative tool is available. However, mere access to a tool does not justify its use. Incorporating expanded access data without thoroughly considering the ethical ramifications may lead to regrets or unintended consequences that are difficult to rectify post-hoc, and we examined these concerns in the last Part of this thesis.

♠

The shifting view on expanded access from solely a treatment modality to also a research opportunity raises concerns. To fully leverage expanded access data, and considering that companies, regulators, and payers often rely on and actively seek such data, it is imperative to proactively address a wide range of ethical and practical considerations that are central to the future of expanded access. These considerations include critical aspects such as data quality, clinical development, financial compensation, and research oversight, among others. In **Part IV**, we clarify the changing role of expanded access from an ethical standpoint, contending that expanded access encompasses both treatment and research. The balance between the advantages of generating evidence and the added burdens of collecting data placed on patients and physicians to conduct research depends in part on the context in which expanded access data are evaluated. Recognizing that the value of such data might be limited compared with conventional clinical trials, it is important to highlight that they can still effectively complement other sources of real-world evidence. We have shown that this is particularly relevant for generating data for academic publications, reimbursement decisions, and providing additional evidence in rare disease contexts.

To this day, legislation surrounding expanded access and its research remains inconsistent among lawmakers. This creates confusion for patients, physicians, regulators, and industry, potentially impeding access rather than expediting it. We provide examples of inconsistent views across regulators, particularly in Europe, and we propose to implement a unified expanded access pathway to enhance regulatory harmonization in the European Union. Furthermore, we advocate for clear guidance on expanded access research by regulators such as the FDA and EMA, including reporting requirements to prevent publication bias, minimal data standards to ensure high data quality, and the inclusion of expanded access data within real-world evidence frameworks, to help clarify when it is appropriate to use these data and when it is not. Such improvements should ensure equitable patient access is tied with robust evidence generation, paving the way to expanded access for patients in need of treatment now, and for future patients to come.

DISCUSSION

This thesis is the result of several studies in which various aspects of expanded access to unapproved medicine have been investigated. The consequences and limitations of all individual studies, such as methodological flaws or limited research scope, have been addressed in the corresponding papers. These concerns are further elaborated on in the introductory prologues and concluding epilogues of the individual Parts (if applicable), providing context and scope for each of our research questions.

This discussion will be dedicated to debate persistent overarching issues, such as the buzz around real-world data, the artificial separation between research and treatment, and the potential benefits and drawbacks of public-private partnerships. Lastly, we suggest promising directions of future research and set realistic expectations for expanded access as it continues to evolve and straddle the line between clinical practice and scientific conduct.

Unmasking the hype: misconceptions on 'real-world data'

During our investigation into the value of expanded access data, the interest in 'real-world data' was on a rise.[1] A search of PubMed reveals that in 2010, 562 articles were indexed for real-world data, which increased more than twofold in 2014 to 1,243 publications, followed by a substantial upsurge to 2,421 in 2018 and a staggering 9,268 articles in 2022. We gratefully capitalized on this trend, as it is undeniable that the term 'real-world data' holds significant appeal. After all, who would prefer to use 'fake-world data'? The success of popular expressions as 'precision' medicine or 'targeted' therapies is fueled by the fear for their antonyms,[2] the underlying notion that no one wants their drugs to be 'imprecise' or 'off-target'.[3]

However, epidemiologists and biostatisticians have been scrutinizing non-interventional data for several decades, advancing designs like case-control, case-cohort, propensity score analyses, or target trials, to partly attenuate biases and produce replicable results, but lacking a fancy term to market their ideas.[4] The concerns that trial results do not provide information on real-world usage are, in my opinion, in part, based on misunderstanding about trials.

One common misconception about clinical trials is that they are based on random sampling, when in fact they are based on randomization.[5,6] Trials enroll patients who volunteer, creating a selection bias. Real-world data does not necessarily solve this 'issue' as it too does not ensure random sampling. For instance, expanded access programs may disproportionately include well-connected, affluent, healthy individuals, further clouding the estimate of drug outcomes in 'real-world' populations.[7] Addressing the issue of selection bias requires more than merely increasing patient numbers. If bias is present, large numbers will simply perpetuate that bias throughout the study design.

However, it is important to note that clinical trials have different objectives, which often do not revolve around achieving random sampling or generalizability.[8] Note that our novel statistical methodology similarly avoids the focus on generalizability: we expand the trial analysis with expanded access data from the patients that are similar to the trial patients.[9] Clinical trials are designed to produce specific outcomes, to conduct an experiment, and careful patient selection is essential to this objective. So, if clinical trials do not primarily address selection bias or generalizability, what is their main focus?

Trials are meant to yield estimates of comparisons - relative effects - which do not provide direct information on absolute effects in populations outside of trials.[9] Patient characteristics are controlled to reduce variation in the estimate of relative effects. Although it is common and expected that subgroups experience different *absolute* effects (e.g., men versus women, young versus old), *relative* effects remain surprisingly stable across subgroup analyses.[5,10] The premise of real-world data relies in part on the misunderstanding that trials would yield absolute, rather than relative effects, and that these relative effects would not be generalizable to populations outside the trial.

For regulatory purposes, establishing relative effects through randomized clinical trials is usually sufficient. However, relative effects may not be the primary interest for reimbursement bodies,[11,12] which require absolute effects to calculate health expenses or budget impacts, or for patients, who may prioritize absolute effects. Modelling can subsequently be used to translate relative effects in absolute terms for groups that were not included in the trial, potentially aided by data of patients not in the trial.[13] It is precisely here where the benefits of real-world data come into play: to aid, or to yield estimates of parameters that cannot be estimated from the trial without bias (e.g., treatment adherence).[14] Confirming this reasoning, our empirical results have shown that reimbursement bodies hence more frequently employ data from expanded access programs than regulators.[15]

Beyond binary thinking: multifaceted perspectives

A recurring concept in the literature on expanded access is that 'Expanded access is treatment, not research'.[7,16,17] Indeed, the primary intent of expanded access is to provide a treatment option for patients in need. However, this persistent 'treatment versus research' mantra presents a false dichotomy. Can methods providing treatment not simultaneously facilitate data collection? With the unprecedented growth of electronic health data, a plethora of 'real-world data' sources initially designed to furnish treatment - such as patient charts, electronic health records, and claims and billing databases - can now be used for research purposes. Despite not being originally intended for research, these sources are increasingly being harnessed for scientific ends.

The distinction between treatment and research should be perceived as a continuum rather than a binary choice,[7,18] acknowledging the potential of goals and functions in the context of data collection and patient care. In fact, I view clinical evidence as existing along a continuum, ranging from randomized clinical trials to single-arm trials, to expanded access programs, to electronic health records, and even to mining social media for data. This spectrum is depicted in Figure 1. The perceived benefits of expanded access data can vary depending on one's perspective. While acknowledging that the value of such data may be constrained in comparison to traditional clinical trials, it is noteworthy that they can still meaningfully augment other sources of real-world evidence.

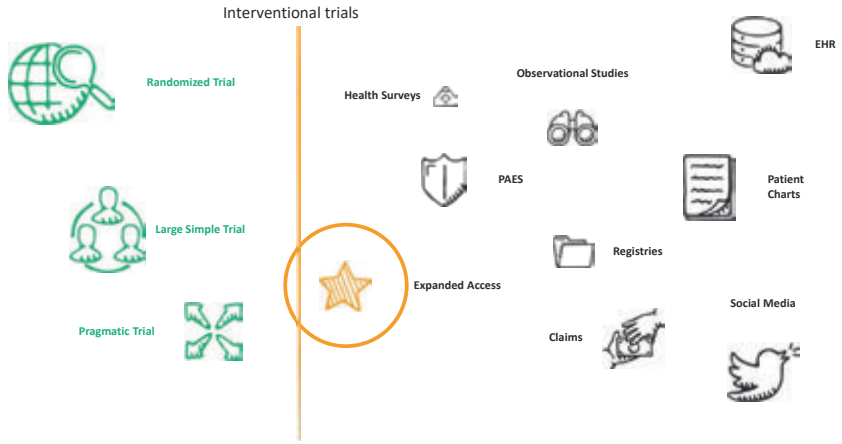

Figure 1: The continuum of data sources from strictly controlled and research-intended, to more treatment-focused.

The rigid categorical approach to continuous concepts can even hinder efficient analysis and data collection, particularly in the context of expanded access programs.[19,20] Some regulators only permit the collection of safety data in these programs, while prohibiting the collection of efficacy data.[20] Despite theoretical refutations to this separation, practical challenges complicate differentiating safety from efficacy, benefit from risk. In fact, 'lack of efficacy' is recognized as an official *safety* warning in pharmacovigilance terminology, as per the Medical Dictionary for Regulatory Activities.[21] Hence, monitoring safety becomes difficult when such efficacy data cannot be collected. Similarly, deaths are considered safety events – but in most (expanded access) settings, survival is also the primary outcome of efficacy. Shifting focus towards the overlap among concepts rather than disparities, can facilitate data collection in expanded access settings.

Future research

Several areas remain that warrant further investigation. Our research primarily centered on examining the benefits of expanded access in terms of current clinical merit and future knowledge generation, but we did not explore patient preferences. It would be valuable to understand how patients perceive expanded access,[22] the extent to which they are willing to trade-off current and future benefits, and their attitudes towards participating in expanded access research.[23]

The majority of our research has been conducted through quantitative methods, driven by our aim to provide objective and reproducible research to avoid any potential conflict of interest. For several studies, we therefore sought data that was labelled as 'pivotal', 'supportive' or 'safety', 'efficacy', or 'cost'.[15,23] Of note, these labels cannot adequately capture all nuances. By reducing the complex underlying data to these labels, we ourselves are guilty of reducing information dimensions. Although we have sometimes provided qualitative examples to accompany our quantitative findings, future systematic, independent qualitative research could provide useful insights into narrative interpretation of expanded access data.

Lastly, our statistical research aimed provide a first idea of developing statistical methods to particularly accommodate for the inclusion of expanded access data. There are ample opportunities for adjustments and comparisons to be made.[24] As these methods aim to address differences in patient characteristics among trial and expanded access patients, it would be useful to quantify to what extent patients in expanded access differ from trial patients. Although these patients are arguably more 'real-world' than trial patients, this topic has never been adequately researched. One potential approach could be to compare the patient descriptive summaries (e.g., 'Table One') in publications of expanded access programs with the descriptive summaries from clinical trials.

Public-private partnerships: mutual benefits or concern for scientific integrity?

As part of this thesis, the Erasmus MC, the Erasmus University Rotterdam, and myTomorrows engaged in a public-private partnership aimed at facilitating an exchange between private assets such as resources, expertise, and market knowledge of expanded access practices, and academic considerations, including public interest, societal needs, and research integrity.[25] Conducting this thesis part-time enabled me to thoroughly investigate everyday issues that I encountered in my work on an academic level. Although such public-private collaborations are increasingly stimulated,[26] it is worth mentioning that the scientific validity of such public-private collaborations has faced growing skepticism.[27,28] In this context, I delve into whether our research indeed raises similar concerns.

Private companies may have commercial interest in research outcomes, such as owning intellectual property or having a financial stake in commercializing research outcomes. Conflicts between company (shareholder) incentives and academic integrity lurk. But it would be overly simplistic to dismiss all public-private partnerships outright. Not all such partnerships are inherently problematic, and there are means to mitigate the risks associated with conflict of interests.[29]

The collaboration funding this thesis was contractually designed to limit private influence.[25] We relied on the private partner to provide in-depth and practical market knowledge, whist relying on public partners to ensure the subsequent research was conducted independently. We presented our results in peer-reviewed journals to provide an additional safeguard to prioritize scientific merit over commercial interests, and our research has been published in open access papers. myTomorrows was not involved in any of the decisions regarding study design and methodology. We retained full autonomy in disseminating research findings, regardless of the outcome. Exemplary, we repeatedly suggested to harmonize European pathways in favor of patient access,[19,30] even though this goes against the commercial interests of myTomorrows as the company benefits from navigating the complex array of European pathways.

We attempted to adhere to all principles of transparency, publishing all our code to replicate our findings online, and rendering all data sets available upon request to replicate or check our findings. Furthermore, we have declared all potential interests, whether they are directly related or not, as per the relevant journal publication guidelines. These conflicts range from receiving public funding to conduct research or provide financial compensation for travel cost, to receiving salary fees, stock or stock options by myTomorrows, to receiving payments by regulatory bodies and pharmaceutical industry to host educational sessions on expanded access.

In spite of these good intentions, it might be naive to believe all private interests have been diverted. It is exactly through this private experience that our academic research is inspired. The potential for residual conflict of interest should be interpreted by the nature of the field of research. Collaborations in the quantitative fields of research that rely on formal language and verifiable findings, such as mathematics, econometrics, or (bio)statistics, are arguable less susceptible to damage scientific reputation compared with more qualitative fields of research that may rely on interpretation and subjective judgement, such as cultural studies or fiscal policy. Arguably, it can be desirable to nourish public-scientific research in the field of nanotechnology, where the exchange of ideas between universities and chip companies serves a greater public interest. Simultaneously, it can be undesirable for fiscal court rulings to be influenced by the opinions of professors that are simultaneously employed by defendants in the court room that stand to benefit from such rulings. The benefits and risks of such collaborations should be

assessed on a case-by-case basis, instead of being judged solely based on guilt-by-association. It is unnecessary to dismiss private interests if they are in alignment with societal, ethical, and academical principles.

Maintaining a steady grip on the slippery slopes of expanded access

One prominent concern that has not yet been addressed is inherent to expanded access programs, and our research on the value of data generation through these programs may have amplified this issue: expanded access programs may hinder clinical development, as patients could bypass clinical trials or opt to withdraw from them.[17] Patients may not be willing to participate in randomized trials due to the fear of being randomized to a control group, which in the context of expanded access typically consists of standard of care and/or placebo. Despite the fact that some patients actually benefit from being randomized to placebo rather than an investigational agent,[31] patients most probably partake in these trials as a means to access investigational medicine.

Well-connected and privileged patients are potentially more likely to know about the option to circumvent clinical trials and attempt to obtain experimental medicine via expanded access.[7,32] This unease is grounded in reality, with evidence of patients dropping out of trials and seeking participation in expanded access programs.[17] This loophole could lead to delays in recruitment and completion of trials. The ones who lose out are the non-privileged, as they are compelled to endure an extended waiting period until the clinical trial concludes and the drug attains approval, thereby delaying their access to the new treatment. Such a system raises ethical concerns, particularly with regard to distributive justice, as it may compromise the fair and equitable distribution of resources.

Regulators may worry that not only patients but also companies would use expanded access as a bypass to clinical trials, particularly since we have demonstrated their ability to generate data. This fear remains largely hypothetical, as we were unable to identify examples of industry-led bypassing of trials through expanded access programs in the literature. Compared with traditional trials, expanded access programs may be rife with bias and are unable to match the sheer quantity and quality of data generated through trials. As long as regulators require the conduct of regulatory trials and companies primarily aim at obtaining such approval, the likelihood of companies using expanded access data as a backdoor as a means to obtain regulatory approvals is virtually zero.[33,34]

Though the foundational principle of expanded access is that patients should not be eligible for trials initially, we are not arguing against a strawman. The US convalescent plasma expanded access program for SARS-CoV-2 exemplified that this fear is not unfounded.[35,36] With over 105,717

patients enrolled in the program before trials were fully enrolled or completed, not only did it hinder trial enrollment, but the data generated from this program also suggested potential treatment benefits.[37] However, subsequent randomized trials could not confirm that convalescent plasma improved outcomes for inpatient care.[38] This program may not be a representative example of standard expanded access conduct, as the behavior in the face of a public health emergency like COVID-19 does not reflect day-to-day business, and the program was academia-driven instead of industry-led. Nonetheless, this serves as a cautious reminder that expanded access program and their data generation should be carefully defined and implemented prospectively while trials are already underway, and despite the size of the program, randomized trials remain unmatched in their ability to provide reliable estimates.

Navigating the road ahead: realistic expectations

Given the high stakes involved in the expanded access and regulatory approvals, it is irrefutable that actors will invariably try to circumvent regulations. For instance, patients may falsify their eligibility for inclusion in clinical trials or actively seek ways to do so, while companies may attempt to bend the rules to their advantage.[39,40] These challenges are not inherent to expanded access, but rather stem from issues such as inadequate education, clouded moral judgments, or deliberate misconduct. Even though strong regulations and ethical oversight can reduce these occurrences, one should be careful not to base legislative judgement solely on rare exceptions.

Expanded access is by no means a panacea, and it was never intended to resolve institutional issues in drug development.[41] Marginalized groups' inability to participate in trials,[42] the potential exclusion of most patients due to stringent inclusion criteria,[43] and the lack of randomized trials for drug approval are all problems not caused by expanded access and will not be solved through it.[44] Efforts to include diverse populations should combat racism and sexism trial enrolment,[45] pragmatic trials should include a wider variety of patients, and regulators should, where reasonable, enforce the conduct of randomized trials. Even with such improvements, some patients will miss out on trial participation.[7] For these patients, expanded access still has a vital role to play – and evidence to generate.

In an ideal scenario, this thesis would never have been written. In such a world, patients would have unfettered access to registered medicine that are proven to be safe and effective, or could seamlessly participate in randomized trials to evaluate risks and benefits to register novel medicines. However, this ideal remains elusive. Barriers that impede patient access to treatment will likely always exist, stemming from factors such as geography, regulations, gender, economics, race, timing, or simply due to a lack of luck. Access to medicine is not (yet) equitable. Although expanded access in a sense treats the symptoms rather than the disease, it can serve as a valuable

safety net for the people that fall through the cracks of health systems and drug development. We have worked to refine and enhance the vital fallback option expanded access provides. The presence of these closing remarks alone testifies to the writing of this thesis. I hope it has moved us, no matter how marginal, towards achieving equitable access supported by structured evidence generation.

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APPENDICES

NEDERLANDSE SAMENVATTING

Expanded access is een route die patiënten en artsen in staat stelt om niet-goedgekeurde medische behandelingen te verkrijgen. Opgezet in 1987 tijdens de aidscrisis, is dit gereguleerde traject alleen een optie voor patiënten die geen baat hebben bij goedgekeurde geneesmiddelen of bij deelname aan klinisch onderzoek (trials). Door de jaren heen is het belang van expanded-accessprogramma's gegroeid, mede door de toenemende beschikbaarheid van online informatie over de ontwikkeling van nieuwe behandelingen en meer recentelijk door de zoektocht naar behandelingen voor COVID-19.

Persoonlijke motivatie

In mijn baan bij myTomorrows hield ik mij bezig met het ontwerpen en implementeren van expanded-accessprogramma's, met speciale nadruk op de efficiënte verzameling van gegevens en de daaropvolgende analyse voor medische doeleinden. De motivatie voor het onderzoek in dit proefschrift komt deels voort uit de praktische problemen die ik tegenkwam in mijn dagelijkse werk. Oorspronkelijk hoopte ik te kunnen leren over de valkuilen van expanded access van andere onderzoekers, in de ijdele hoop diezelfde fouten te kunnen vermijden.

Al snel ontdekte ik dat er geen uitgebreid of systematisch onderzoek was gedaan naar dit onderwerp. Hoewel er beperkte, anekdotische voorbeelden in de literatuur werden beschreven, was het gebruik van expanded access om gegevens te verzamelen en de verschillende doeleinden waarvoor deze gegevens konden worden gebruikt, zoals beslissingen van wetgevers, publicaties of vergoedingsbeoordelingen, onduidelijk. Bovendien waren expanded-accessprogramma's oorspronkelijk ontworpen om medische behandeling te bieden in plaats van wetenschappelijk onderzoek uit te voeren. Deze mogelijke verschuiving in de aard van deze programma's kan leiden tot ethische bezwaren, zoals of we deze programma's überhaupt moeten gebruiken om gegevens te genereren, onder welke omstandigheden en wanneer. Naast de theorie en ethiek, stonden er ook praktische bezwaren in de weg, zoals de legaliteit van het verzamelen van deze gegevens en wat de waarde zou zijn van deze data wanneer ze eenmaal (legaal) verzameld waren.

Mijn collega's op het werk en mentoren aan de Erasmus Universiteit en het Erasmus MC moedigden me aan om deze zaken op een wetenschappelijke wijze zelfstandig uit te zoeken. Aangezien het huidige werk het resultaat is van onze samenwerking, zal ik vanaf dit punt de term 'wij' gebruiken.

Deze thesis

Het belangrijkste doel van dit proefschrift is om de waarde van expanded-accessprogramma's te achterhalen. We benaderen hierbij het begrip 'waarde' vanuit verschillende perspectieven. Zo kijken we naar het klinische voordeel dat direct kan worden behaald voor huidige patiënten in expanded access programma's. Tegelijkertijd kijken we ook naar de mogelijke baten van gegevensverzameling in expanded access voor toekomstige patiënten. Naast deze kwalitatieve benadering, dienen we ook zorgvuldig rekening te houden met de ethische en beleidsimplicaties van de veranderende aard van expanded-accessprogramma's, naarmate de focus meer verschuift van slechts behandeling naar het tevens verzamelen van gegevens.

We stelden de volgende onderzoeksvragen:

- ♣ Wat zijn de medische voordelen voor patiënten die toegang krijgen tot experimentele behandelingen?
- ♦ Op welke manieren worden gegevens verkregen uit expanded-accessprogramma's gebruikt en door wie?
- ♥ Kunnen bestaande statistische technieken worden aangepast om gegevens van expanded-accessprogramma's op te nemen bij het analyseren van klinisch onderzoek?
- ♠ Welke ethische vraagstukken ontstaan wanneer expanded access wordt gebruikt als middel om bewijs te genereren, en hoe kunnen verbeteringen worden aangebracht in expanded-accessbeleid om die vragen te beantwoorden?

De **inleiding** bevat een kort overzicht van de geschiedenis van expanded access als middel om patiënten toegang te bieden tot experimentele medische behandelingen. Daarnaast bevat zij een gedetailleerde beschrijving - in het Nederlands - van de geschiedenis en wetgeving van expanded access in Nederland. Ter illustratie kunt u lezen over de resultaten van twee verschillende praktijkvoorbeelden van expanded-accessprogramma's:

1. In het eerste programma konden patiënten met oncontroleerbare infecties door herpesvirussen toegang krijgen tot een experimentele antivirale therapie, pritelivir.
2. In het tweede programma konden patiënten met verschillende ziekten gerelateerd aan ongecontroleerde Epstein-Barr-virusinfecties toegang krijgen tot een nog niet-goedgekeurde celtherapie, tabelecleucel.

♣

In **Deel I** hebben we onderzocht hoe vaak experimentele geneesmiddelen doorgaan van een vroege naar een latere onderzoeksfase. Dit is van belang voor expanded access, omdat expanded acces vaak wordt aangevraagd op basis van presentaties van voorlopige bevindingen op wetenschappelijke congressen, waarbij de nieuwe geneesmiddelen vaak als 'veelbelovend' of 'baanbrekend' worden genoemd. De waarde voor patiënten van toegang tot geneesmiddelen in ontwikkeling kan worden afgeschat door te kijken naar de kansen van geneesmiddelenontwikkeling en de veiligheid en werkzaamheid.

Om de reikwijdte van ons onderzoek te beperken, richtten we ons allereerst op het gebied van hematologie. We beoordeelden de klinische voordelen van experimentele geneesmiddelen bij acute myeloïde leukemie met behulp van ziekte-specifieke schalen die ontwikkeld zijn om de mate van werkzaamheid van oncologie- en hematologiegeneesmiddelen te evalueren. Zowel oncologie als hematologie zijn vakgebieden met een hoge 'unmet medical need' (onvervulde medische behoeften, ziektelast), en daarom trekken ze een aanzienlijk aantal expanded-accessverzoeken aan.

Daarnaast gebruikten we een universele maatstaf voor toegevoegde gezondheidswaarde die het mogelijk maakt om verschillende medicijnen voor verschillende ziektegebieden met elkaar te vergelijken, verdergaand dan hematologie en oncologie. De Quality-Adjusted Life Year, of QALY, is een maatstaf die vaak wordt gebruikt in kosteneffectiviteitsonderzoek om de toegevoegde voordelen van geneesmiddelen te bepalen voordat ze worden vergoed in het Verenigd Koninkrijk. In Nederland doet het Zorginstituut Nederland vergelijkbaar onderzoek, om te kijken of geneesmiddelen in aanmerking komen voor opname in het basiszorgverzekeringspakket.

We concludeerden via beide onderzoekspaden dat de gemiddelde klinische waarde van nieuwe geneesmiddelen in ontwikkeling hooguit bescheiden is. Uit deze resultaten kan het lijken dat de kans voor patiënten om aanzienlijke klinische voordelen te behalen uit expanded-accessprogramma's beperkt is. De werkelijkheid kan echter positiever uitpakken, aangezien artsen en patiënten mogelijk meer geneigd zijn om deel te nemen aan expanded-accessprogramma's, en bedrijven eerder bereid zijn om dergelijke programma's te starten, voor effectievere geneesmiddelen dan voor minder effectievere geneesmiddelen. Naar minder effectieve middelen is simpelweg minder vraag. Deze redenering zou impliceren dat expanded access toch tot een grotere kans op een klinisch positief resultaat voor huidige patiënten. Bovendien, en met name interessant in dit proefschrift, kunnen er voordelen worden behaald door het analyseren van gegevens van huidige expanded-accesspatiënten om de medische wetenschap te bevorderen voor toekomstige patiënten.

Het verzamelen van kennis via expanded-accessprogramma's vormde derhalve de basis voor ons daaropvolgende onderzoek in **Deel II**. Toen we aan dit proefschrift begonnen, was informatie over het gebruik van gegevens uit expanded-accessprogramma's voornamelijk anekdotisch. Er wordt verplicht toezicht gehouden op de veiligheid van geneesmiddelen in expanded-access programma's (farmacovigilantie), maar informatie over de werkzaamheid, data over effectiviteit, werden niet systematisch gedocumenteerd en deze praktijk werd door sommigen als onmogelijk of onethisch beschouwd.

Om erachter te komen of en hoe expanded-accessdata al gebruikt werden, ontwikkelden we algoritmen om de systematische analyse van een groot aantal gezondheidsbeleidsdocumenten mogelijk te maken. Hierbij moesten we soms geavanceerde technieken inzetten, zoals optische tekenherkenning, die voor de computer niet direct leesbare afbeeldingen (scans, gefaxte brieven) om kon zetten in tekstgegevens. Deze geautomatiseerde aanpak stelde ons in staat om grote volumes documenten te doorpluizen die online beschikbaar zijn bij toezichthouders zoals de Amerikaanse FDA, de EU EMA en kosteneffectiviteitsonderzoeksinstituten zoals NICE in het VK.

Voor zover wij weten presenteerden wij de eerste systematische overzichten van het gebruik van expanded-accessgegevens in **Deel II**. Om deze resultaten voor iedereen toegankelijk te maken, hebben we online onderzoeksvideo's en animaties gemaakt om onze openbaar beschikbare code uit te leggen en de wetenschap erachter inzichtelijker te maken.

We ontdekten dat het gebruik van gegevens uit expanded-accessprogramma's in de loop van de tijd is toegenomen, niet alleen door toezichthouders, maar ook door vergoedingsinstanties en onderzoekers. Gegevensverzameling is niet langer beperkt tot informatie over veiligheid (safety), maar is uitgebreid met informatie over werkzaamheid (efficacy), door patiënten gerapporteerde resultaten (patient-reported outcomes) en zelfs zorgkosten. Mede door ons onderzoek is duidelijk geworden dat het gebruik van expanded-accessdata veel vaker voorkomt dan gedacht en zeker niet slechts anekdotisch is. Deze data spelen soms een substantiële, en mogelijk zelfs systematische rol bij het genereren van betrouwbaar bewijs voor de veiligheid, effectiviteit, en kosten van geneesmiddelen. Met deze nieuwe kennis in ons achterhoofd richtten wij ons op het praktische aspect van het statistisch combineren van deze expanded-accessdata met data uit klinische trials.

♥

Expanded-accessprogramma's kunnen aanvullend bewijs leveren dat is verkregen via regulatory trials, maar beide worden vaak afzonderlijk geanalyseerd. In **Deel III** hebben we een nieuwe statistische techniek ontwikkeld om tegelijkertijd bewijsmateriaal uit beide gegevensbronnen te verwerken. Door Bayesiaanse statistische methoden die informatie uit eerdere gegevens

proberen lenen ('dynamic borrowing methods'), te combineren met technieken die bias tegengaan ('propensity scores'), hebben we geprobeerd de invloed van ongemeten en gemeten verstorende variabelen ('confounding variables') te beheersen.

Op dezelfde manier als hoe onderzoekers hebben geprobeerd om informatie over historische controlegroepen op te nemen in de huidige controlegroep van een trial, hebben we aangetoond dat het mogelijk is om informatie van huidige expanded-accessbehandelingsgroepen op te nemen in de huidige experimentele behandelgroep van een trial. Onze methode is geïllustreerd door individuele patiëntdata uit de trials en expanded-accessprogramma's te verkrijgen en te analyseren van patiënten die vemurafenib kregen toegediend, een behandeling voor borstkanker.

Waar de interpretatie van expanded-accessgegevens tot nu toe kwalitatief was, hebben we nu een kwantitatief hulpmiddel beschikbaar gesteld. Maar omdat we nu een hamer hebben, moeten we niet overal spijkers zien. Er gaan zowel ethische als statistische risico's gepaard met het gebruiken van expanded-accessdata. Het opnemen van die gegevens zonder de ethische implicaties zorgvuldig in overweging te nemen, kan onbedoelde gevolgen hebben die moeilijk achteraf te herstellen zijn. 'Bezint eer ge begint' luidde daarom het credo van het laatste deel van mijn proefschrift.

♠

Het veranderende perspectief op expanded access van alleen een behandelingsmodaliteit naar ook een onderzoeksmogelijkheid roept zorgen op. Om expanded-accessgegevens volledig te benutten en terwijl bedrijven, toezichthouders en betalers (zoals zorgverzekeraars) steeds vaker vertrouwen op en actief op zoek zijn naar dergelijke gegevens, is het noodzakelijk om proactief een breed scala aan ethische en praktische overwegingen te bespreken die centraal staan in de toekomst van expanded access. Deze overwegingen omvatten aspecten zoals gegevenskwaliteit, klinische ontwikkeling, financiële compensatie en toezicht op medisch onderzoek.

In **Deel IV** gaan we dieper in op de veranderende rol van expanded access vanuit een ethisch oogpunt. We stellen we dat expanded access niet óf onderzoek óf behandeling is, maar zowel behandeling als onderzoek omvat. De balans tussen de voordelen van het genereren van extra data, en de lasten voor patiënten en artsen die ermee gepaard gaan om zulk onderzoek uit te voeren, moeten zorgvuldig tegen elkaar worden afgewogen.

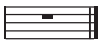
De waarde van expanded-accessgegevens is beperkt als men deze vergelijkt met gegevens uit gerandomiseerde studies. Maar deze data blijken zeer waardevol te kunnen zijn in vergelijking met andere bronnen van medisch bewijs, zoals elektronische patiëntendossiers of zorgverzekeringsdata. We hebben aangetoond dat expanded-accessdata met name nuttig zijn

bij het opstellen van academische publicaties, het nemen van vergoedingsbeslissingen en het aanvullen van medisch bewijs voor (zeer) zeldzame ziekten.

Desalniettemin varieert de wetgeving met betrekking tot expanded access (en het bijbehorende onderzoek) sterk tussen wetgevers. Dit schept verwarring voor patiënten, artsen, toezichthouders en de industrie, wat mogelijk de toegang voor patiënten eerder in de weg staat dan versnelt. In dit laatste deel geven we ook enkele voorbeelden van inconsistente standpunten tussen toezichthouders, met name in Europa, en we stellen voor om een uniforme expanded-accessroute te implementeren om de wetgeving in de Europese Unie beter op elkaar af te kunnen stemmen.

Tot slot pleiten we voor duidelijke richtlijnen over expanded-accessonderzoek door toezichthouders zoals de FDA en EMA. Hieronder zouden bijvoorbeeld publicatie-eisen om selectieve rapportage te voorkomen kunnen vallen, of een handleiding voor minimale datakwaliteit om een hoge gegevenskwaliteit te waarborgen. Daarnaast zou expanded access expliciet kunnen worden benoemd als potentiële bron van medische informatie, en hoe deze informatiebron zich verhoudt tot bijvoorbeeld single-arm trials, retrospectieve studies van elektronische patiëntendossiers, of registerdata.

Op deze manier wordt het voor artsen, patiënten, en de industrie duidelijk waar expanded access past in het grotere plaatje van medische bewijsvoering, en wanneer het passend is om deze gegevens te gebruiken en wanneer niet. Dergelijke verbeteringen moeten een eerlijke toegang voor patiënten waarborgen in combinatie met robuuste bewijsvorming, en zo de weg vrijmaken voor patiënten die nu behandeling nodig hebben via expanded access, maar ook voor patiënten die hier in de toekomst baat bij kunnen hebben.



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PORTFOLIO

PhD Candidate	Tobias Boy Polak Department of Biostatistics & Epidemiology, Erasmus Medical Center Rotterdam Department of Health Technology Assessment, Erasmus School of Health Policy & Management, Erasmus University Rotterdam
PhD Period	2019-2023 external doctoral candidate (one day a week)
Promotor	Prof.dr. Carin Uyl – De Groot
Copromotor	Dr. Joost van Rosmalen

Presentations

1. May 21, 2019. CBI Managed Access Programs and Accelerated Pathways, **Amsterdam**, The Netherlands. Title: Using Data from EA Programmes for Regulatory Approvals: Analysis of EMA and FDA over the years. **Oral**.
2. February 20, 2020. Expanded Access Summit 3.0, **Washington DC**, USA. Title: Getting past the simple narratives. **Panel**.
3. February 2020. Seminar Series Working Group on Ethics and Real-World Evidence, New York University Grossman School of Medicine, dep. Population Health. **New York City, New York**, USA. Title: Future of Expanded Access Research. **Invited International Speaker**.
4. February 12, 2020. CQM Seminar Department of Biostatistics and Epidemiology, Erasmus University Rotterdam. **Rotterdam**, The Netherlands. Title: Expanded Access and Real-World Data. **Internal Seminar Series.**
5. December 7, 2020. Regulatory Science Network Netherlands. Virtual (online). Title: Leveraging the value of collaboration - from regulatory science to regulatory innovation. **Invited Speaker.**
6. October 16, 2022. World Orphan Drug Conference, **Barcelona**. Title: Generating Evidence through Compassionate Use of Rare Disease Drugs. **Oral**.
7. October 10, 2022. Seminar Series Working Group on Ethics and Real-World Evidence, New York University Grossman School of Medicine, dep. Population Health. **New York City, New York**, USA. Title: Exploring the value of Real-World Data in Expanded Access Programs. **Invited International Speaker**.
8. October 27, 2022. Biostatistics Seminar Series. Department of Biostatistics and Epidemiology, New York University Grossman School of Medicine, dep. Population Health. **New York City, New York**, USA. Title: Augmenting Treatment Arms Through Propensity-Scores and Dynamic Borrowing: An Application to Expanded Access Programs. **Invited International Speaker**.

9. June 29, 2022. BioBusiness Summer School, Amsterdam University, **Amsterdam**, The Netherlands. Title: Expanded Access. **Invited Speaker**.
10. June 1, 2022. CQM Seminar Department of Biostatistics and Epidemiology, Erasmus University Rotterdam. **Rotterdam**, The Netherlands. Title: "The use of Propensity Scores in Dynamic Borrowing". **Internal Seminar Series.**
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3. Visiting Scholar to New York University Grossmann School of Medicine, Working Group on Compassionate Use & Preapproval Access (CUPA), September 2022 – January 2023.

ABOUT THE AUTHOR

Tobias Boy Polak was born on December 30th, 1993 in Dordrecht. In 2011, he completed his gymnasium education with honors at the Lorentz-Casimir Lyceum in Eindhoven. The following year, he started his study in Econometrics and Operations Research at the Erasmus University in Rotterdam. He briefly studied Latin and Greek concurrently at Leiden University, but decided to concentrate on econometrics. He pursued a minor in Applied Statistics, Mathematics, and Informatics in the Social Sciences at the University of Aix-en-Provence. Graduating with honors, Tobias earned his Master's degree in Econometrics and Management Science, focusing on Business Analytics and Quantitative Marketing. His master's thesis was supervised by Prof. Dr. Dimitris Rizopoulos and Dr. Joost van Rosmalen at the Department of Biostatistics at Erasmus Medical Center, and Prof. Dr. Dennis Fok and Prof. Dr. Richard Paap at the Econometric Institute at Erasmus University Rotterdam.

During his studies, Tobias maintained a NOC*NSF Topsport status as a member of the Dutch Youth Bridge Team, winning eight gold medals at Dutch Championships and two silver medals at the World Championships. After concluding his studies and bridge career Tobias started working at myTomorrows, a company specializing in expanded access services. In 2019, he assumed dual roles, serving as both the Director of Real-World Data at myTomorrows and as an external PhD candidate for one day per week. As part of his PhD trajectory, he was invited to attend New York University Grossman School of Medicine as a Visiting Scholar to the Compassionate Use and Preapproval Access (CUPA) working group at the Division of Medical Ethics with Dr. Art Caplan, Dr. Alison-Bateman House, and Dr. Hayley Belli, in 2022. Tobias is a member of CUPA's working group on Ethics & Real-World Evidence. He obtained funding for his research through a HealthHolland Public-Private Partnership Grant and a Prins Bernhard Cultuurfonds Grant to support his Visiting Scholarship in New York City.

Tobias lives in Rotterdam with his first husband. During his leisure time, he enjoys engaging in various sports, attending classical music concerts and theatrical performances. As a hobbyist, he participates in a musical theatre group and a classical choir.

DANKWOORD

Het schrijven van deze thesis is niet onopgemerkt gebleven bij de mensen die mij omringen. Sterker nog, dit werk zou in zijn geheel niet tot stand zijn gekomen zonder hun steun en bijdrage. Ik wil specifiek enkele mensen bedanken die een onmisbare rol in dit proces hebben gespeeld.

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It is with an enduring sense of appreciation that I reflect on my time as a Visiting Scholar at New York University, a cherished opportunity made possible by dr. Alison Bateman-House, dr. Hailey Belly, and Prof.dr. A. Caplan. The friendships I fostered with the other CUPA group members (e.g., Lisa, John, Tamar), and the welcoming ambiance (and carpool karaoke) provided by the Voorham family have ingrained an affection for the City and 69th Street that will forever reside in my heart.

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HTA. Ondanks dat zijn voetstappen niet meer op de universiteitsgangen hoorbaar zijn, wil ik in het bijzonder Matthijs Versteegh noemen als initiële bron van inspiratie. Daarnaast stonden Jolien Roos en Dimitris Rizopoulos aan de wieg van deze thesis.

Waar zou dit proefschrift zijn zonder myTomorrows? De vrijheid om een deeltijdpromotie aan te gaan en de professionele ervaring van het helpen van patiënten en cliënten met expanded access vormen het fundament van dit werk. Maar nog meer putte ik energie uit alle enthousiaste en unieke Mighties. In het bijzonder noem ik de mensen van het eerste uur (Dennis, Karlijn, Michel, Bart, Laura), de inspiratoren (Ronald, Remco, Alice, Robert-Jan) en mijn directe collega's: Sarah en Jasmin. Deze ervaring was onvergetelijk en ik blijf jullie nauwgezet volgen.

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In het leven naast mijn werk en promotie verzorgde met name Tom mij afleiding in bridge, tezamen met Wubbo & Agnes, Bas, Bert, Harm, Anton, Simon, en de vele andere (jeugd)bridgers van BC'70, de Lombard en HOK. Toen ik de kaarten aan de wilgen hing bracht muziek een welkome afleiding: de ontelbare bezoeken aan de Doelen, en de verwoede pogingen datzelfde podium te betreden. De zanglessen, musicals, en kooroptredens, maar ook de soirées aan de Heemraadssingel of het kraken van menig valse noot bij karaoke of Gay Pride met mijn stiefzusters hebben mijn promotietijd verlicht.

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Mijn familie: alle neven, nichten, ooms en tantes Polak, Schuurink en Teeling.

Mijn broers Jurriaan en Kylian, die al vanaf het begin met mij opgescheept zitten. Ook al konden we elkaar wel eens kielhalen, we lieten elkaar nooit zinken. Hoe fortuinlijk ben ik om naast jullie op te mogen groeien. Met Freya, Floor en Felix wordt dat geluk alleen maar groter.

Papa en mama, ik prijs mijzelf gelukkig met jullie liefde, trots en onvoorwaardelijke steun. Het warme bad van ons gezin heeft mij in staat gesteld boven te komen drijven, soms te vliegen, maar toch weer met beide voeten op de grond te komen. Bedankt voor het creëren van een thuis, een veilige haven. Waarheen ik ook dobber, de Sampan vaart vlak achter mij.

Lieve schoonmoeder, lieve Liesbeth, vanaf het eerste moment bij jou heb ik mij welkom gevoeld. Dank voor je oprechte interesse en het voortbrengen van de grootste bron van geluk in mijn leven.

David, mijn grote liefde en echtgenoot. Zonder jou zou dit proefschrift een onvervulde droom zijn gebleven. Welk duo zou standhouden na het schrijven van tien gezamenlijke artikelen? Maar deze wetenschappelijke bijdragen vallen in het niet bij de liefde, warmte en stabiliteit die ik ervaar zodra jij in de buurt bent. Jij brengt de melodie in mijn leven, leert mij te tellen, te rusten en maat te houden. Samen bouwen we een orkestje met onze olifantenfamilie. Ik verlang ernaar om nog vele jaren met jou te blijven dansen, op de harmonieën van onze eigen muziek.