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Research

ROLE OF POST APPROVAL CLINICAL TRIALS FOR DRUG SAFETY

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Abstract

Following the drug-approval process, concerns remain regarding the safety of new drugs that are introduced into the marketplace. In the case of rare adverse events, the number of subjects that are treated in randomized controlled trials is invariably inadequate to determine the safety of the new pharmaceutical. Identifying safety signals for new and/or existing drugs is a major priority in the protection of public health. Unfortunately, design, analysis, and available data are often quite limited for detecting in a timely fashion any potentially harmful effects of drugs. In this review, we examine a variety of approaches for determining the possibility of adverse drug reactions. Our review includes spontaneous reports, meta-analysis of randomized controlled clinical trials, ecological studies, and analysis of medical claims data. We consider both experimental design and analytic problems as well as potential solutions. Many of these methodologies are then illustrated through application to data on the possible relationship between taking antidepressants and increased risk of suicidality.

Keywords: Poisson regression, propensity scores, adverse events, meta-analysis, mixed-effects models, suicide

INTRODUCTION

Post-marketing studies are a major activity in the life cycle of a licensed drug/medicinal product and are regularly conducted by pharmaceutical companies and contract research organisations. Regulatory agencies rely on such industry funded studies for surveillance of drug safety. In particular, the detection of “rare” (1 in 1000) and “very rare” (1 in 10 000) adverse drug reactions is often possible only with post-marketing studies.[1]

According to the German Medicinal Products Act (Arzneimittelgesetz, AMG) all companies initiating a post-marketing study in the German drug market are required by law to register their study. The act specifies that the purpose of such studies is to investigate the use of medicinal products in daily routine, to assess rare adverse drug reactions, and to improve long term drug safety.[2] To our knowledge there is no such law in other countries requiring

all post-marketing studies to be registered, and there is considerable variation in the definition of such studies and the scope of registration in other EU countries.[3] In this context, it should be of note that drug licensing and pharmacovigilance activities have been harmonised in the EU since 2001.[4]
In the US, regulatory approval and registration of some post-marketing studies is required (such as interventional studies that must be registered under the US Food and Drug Administration Amendments Act of 2007[5]), but, unlike Germany, not all post-marketing studies have to be registered.
In light of the documented lack of knowledge about rare adverse drug reactions from pre-marketing randomised controlled trials[6] and systematic under-reporting of spontaneous reporting schemes,[7] German regulators,[8] physician bodies,[9,10] and statutory health insurers [11] have re-emphasised the importance and necessity of post-marketing studies for evaluating newly authorised drugs.
Despite Germany requiring the registration of all post-marketing studies, little is known on their size, cost, and nature. We therefore initiated freedom of information requests to obtain registration documents to understand the current state of post-marketing studies and evaluate whether these studies meet the aims specified in the Medicinal Products Act, particularly their potential to assess rare adverse drug reactions and thus help improve long term drug safety.

Randomized controlled trials (RCTs) have been considered the gold standard to demonstrate efficacy since the 1960s.[12,13]While current routes to market for investigational drugs typically require at leasttwo pivotal RCTs, these are time-consuming, costly, and produce evi-dence that can have limited applicability in real-world clinical practice. There is, therefore, a move towards investigating innovative ways to improve the efficiency of clinical research.[14,15]

The controlled nature of an RCT offers advantages in evidence generation as there are standard methods to reduce bias (like random-inaction and blinding), and they have comprehensive measurement of outcomes to demonstrate efficacy against both active and placebocontrols.[16]

However, RCTs do not accurately reflect real-world circumstances under which patients are treated; thus, there is often need for observational studies to support additional evidence generation, particularly around questions of safety. Real-world data (RWD) forms the basis for real-world evidence(RWE) and can be extracted from a broad range of sources such as patient registries, health care databases, claims databases, patient net-works, social media, and patient-generated data from wearables.[17-20]The definitions of RWD and RWE are relatively consistent between key regulatory agencies (see Table 1).[21]

While RWE from observational studies is well accepted for post-approval safety monitoring and to answer pharmacy economic questions3,[22,23] its contribution to regulatory decisions around effectiveness has been more limited. Indeed, evidence quality can be compromised by confounding by indications or a general lack of rigorous collection standards. There is, therefore, a need for the development of novel trial methodologies that can take the best parts of traditional RCT and observational study designs to produce RWE that provides adequate scientific evidence for regulatory decision-making. It has already been recognised byhealth authorities that there is a wide spectrum of potential uses ford/RWE in clinical studies, some of which preserve key features such as randomization.

THE EMERGING RULES FOR RWE THATIS FIT FOR REGULATORY PURPOSES

The 21st Century Cures Act and PDUFA VI requires the FDA to accelerate drug development and approval processes, and more specifically, to produce guidance on how to incorporate patient perspectives and innovative study designs, including RWE, into the drug development process. The recently published FDA framework for evaluation of how RWE can be incorporated into the regulatory approval process highlights the key topics for which full evaluation will be undertaken.

There is a need to define the rules for RWE that is fit for regulatory purposes. However, while the development of innovative trial designs is being actively encouraged by the major regulatory agencies, particularly with the FDA's Complex Innovative Trial Designs Pilot Program and Clinical Trials Transformation Initiative and the EMA's adaptive pathways initiative, the required standards to produce RWE that is acceptable for regulatory decision-making havenot yet been fully defined. Although regulators are open top roposals for studies with RWD and receiving RWE, the decision topursue an innovative study design as part of a clinical development program and regulatory approval strategy is not straightforward, asthe routes to obtaining pilot guidance are complex and the“rules”for acceptance of evidence in regulatory decision-making are not yet firmly defined. It is therefore essential to engage with regulatory authorities early to obtain alignment on objectives, inform the studydesign, and

ensure the study design and data are acknowledged as“fit-for-purpose”before conducting a study that may not meet the regulatory goals.

To aid this process, several stakeholders have published frame-works and recommendations for the creation of RWE suitable for use in regulatory decisions. The Duke-Margolis Center for Health Pol-icy, with support from the FDA, released a white paper on the regulatory use of RWE in 2017 following open consultation with academics, patients, and industry.48Emphasizing considerations for developing RWE that is fit for regulatory purposes, they identified several areas for practical improvement, including the need to ensure that the appropriate RWD sources are matched with appropriate study designsand data collection and handling methods to address the research question. They also encourage the formation of transparent collaborations and the sharing of datasets. Professional societies have also weighed in here too, with the International Society for Pharmaco economics and Outcomes Research and the International Society for Pharmacoepidemiology publishing recommendations forgood procedural practices for RWE, aiming to build trust and expandits current use in health care decision-making.Many of the recom-mendations made in these aforementioned publications have beenformalized in the FDA framework document.

An important part of planning innovative studies to produce RWE that provides adequate scientific evidence for regulatory decision-making is preparation of a thorough analytical plan at the outset ofthe study. This is already an integral part of most traditional pivotaland post-safety trials and should reasonably be extended to effective-ness studies that use RWD. Some also argue that pivotal and safety outcome RCTs and observational post authorization safety studies should be registered on appropriate repositories (eg, ClinicalTrials.gov or the EU PAS Register) prior to study initiation as a requirementof the regulatory process. Whether RWE studies will be required to beregistered in such a way is a topic of ongoing debate, with opinionsharply divided. Registration by itself is no guarantee of study quality,and any benefit from registration would be heavily dependent on whatinformation would be required to be posted (eg, study protocols,methodological details, etc.). Further discussions between stake-holders will be required before a consensus develops.

In a separate framework on the regulatory use of RWE, Dreyer(2018) has discussed the requirement and transferability of key RCTstudy design elements to real-world studies. This builds on the cur-rent thinking around clinical outcomes from RWD analysis, suggest-ing that outcomes should be patient-centric and should beobservable and relevant to daily clinical practice. Specific issues areaddressed, such as blinding, which is routinely used in RCTs, but isoften impractical to achieve under“real-world”circumstances, espe-cially when comparing pharmacologic and nonpharmacologic treat-ments and when using a selection of“standard of care”comparators, which differ by locale, and while informative, wouldbe impossible to blind. Furthermore, blinding might not be necessaryfor objective outcomes such as the results of a blood tests and imag-ing, for example, where in most cases, third-party raters, such aspathologists, are essentially blinded to treatment.The importanceof using data sources that are“fit for purpose”and the familiarityof researchers with potential sources of bias or error so that themost appropriate study methodology is employed is also emphasized.Analytical methods should be transparent, defined up front, and opti-mized to answer the research question.

Regulators and industry have acknowledged the value of scientifi-cally rigorous and innovative study methodologies as the key route toachieving the standard of substantial evidence for RWE.As ameans to achieve this, the FDA framework proposes that the follow-ing should be considered: (a) whether the RWD are fit for use; (b)whether the trial or study design used to generate RWE can provideadequate scientific evidence to answer or help answer the regulatoryquestion; (c) whether the study conduct meets FDA regulatoryrequirements (eg, for study monitoring and data collection).8It shouldbe noted that strict applicability of these rules, particularly for moni-toring, is rarely feasible for studies that rely on existing data, sincethe identities of patient and care providers are masked to protect pri-vacy in most secondary data sources.

Similarly, the EMA in its recent report on the use of large datasetsfor RWE made several recommendations to improve the quality ofRWE, including the need to define standard formats for documentingdatasets, protocols, and tools used to ensure study reproducibility. Inaddition, it emphasizes the need to ensure that outcome measuresfrom novel data sources such as wearables should be reflective of adefined clinical benefit.If these considerations and recommenda-tions are fully addressed by novel study methodologies, the qualityof RWE will improve, and studies using RWD could increasingly beused in support of decisions about therapeutic effectiveness. Thedevelopment of sufficiently robust RWE will ultimately depend onthe ability of experts such as pharmacoepidemiologists, statisticians,data scientists, and academics to develop these new methodologiesto optimize hybrid study designs, RWD collection and analysis in away that is compliant with our current understanding of best practicefor RWE

generation, and open to regulatory scrutiny.Sponsors anddata owners should proactively identify and develop standard operating procedures to be prepared for FDA audits and oversight bydefining requirements for record retention, auditing, and patientprivacy.

MODERNIZING THE CLASSICAL RCT

Some specific hybrid study designs under consideration for regulatory decision-making by the FDA fall into three broad categories: (a) inves-tigational new drug submissions for RCTs that use RWD to capture clinical outcomes or safety data, including pragmatic and large simple trials; (b) protocols for single-arm trials that use external controls; (c)clinical trials using RWE to fulfil a post-marketing requirement for further evaluation of safety or effectiveness to support a regulatory decision.

AIM AND OBJECTIVE

To enable timely access to innovative drugs, the European Medicines Agency (EMA) can conditionally approve drugs based on a less comprehensive evidence package when immediate availability of the drug outweighs the risks due to the less comprehensive evidence package. Importantly, the benefit-risk balance still needs to be judged positive, but more uncertainty may be considered acceptable in light of the drug's potential to address unmet medical needs.

DISCUSSION

We conducted a prospective, multi centre, open-labeled, randomized superiority clinical trial and hypothesized that Favipiravir would be superior to Arbidol in terms of efficacy for moderate symptoms, and would accelerate the clinical recovery of pyrexia, cough, and breathing difficulties compared with Arbidol.

Favipiravir treatment did not improve clinical recovery rate of Day 7 (61.21%) compared to Arbidol group (51.67%). However, it did significantly improve the latency to cough relief and decreased the duration of pyrexia. Favipiravir was not associated with any differences in ICU admission, AOT/NMV, dyspnea, respiratory failure or all-cause mortality.

Interestingly, post-hoc observation showed that a trend of Favipiravir being effective to improve clinical recovery rate at Day 7 in moderate COVID-19 patients compared to Arbidol. This effect diminished for severe/critical COVID-19 patients. Additionally, post-hoc analysis showed that for moderate COVID-19 patients, Favipiravir was associated with decreased auxiliary oxygen therapy or noninvasive mechanical ventilation rate with marginal significance (P=0.0541). Finally, in the FAS, post-hoc analysis also showed that Favipiravir treatment significantly decreased de novo incidences of dyspnea. Whether Favipiravir would be only effective for moderate COVID-19 patients, or could Favipiravir be used to prevent disease progression, is a question warrant future investigation.

The combination of traditional Chinese medicine and antiviral drugs is more common in China, which is due to the traditional medical culture background of the treatment of choice. Also, anti-infection and immune regulation play an important role in the treatment of the COVID-19. Ancillary treatments, such as traditional Chinese medicine, anti-infection and immune modulatory drugs, were without statistical difference between groups.

Our trial has several limitations. Firstly, for COVID-19, there is no clinically proven effective antiviral drug to serve as the control arm. Although Chinese guideline had recommended several options including Arbidol, no RCT results on these drugs were reported. Arbidol was widely used by Chinese doctors in the beginning stage of this epidemic of COVID-19 (Jan. 1-30, 2020) based on in vitro evidence.12 For ethical reasons, we chose Arbidol for the control arm. Secondly, observation time frame was limited due to the urgency of this epidemic. For the same reason, no relapse (including nucleic acid conversion, pyrexia, cough, or pneumonia progress by radiology) tracking were performed for the discharged patients. Thirdly, in the inclusion criteria, we did not force positive nucleic acid test as a necessity. The accuracy of nucleic acid assay was limited, which might due to multiple reasons including previous treatment, latency of onset, sampling method, biological specimen characteristics. This particular accuracy problem was a known issue among clinical practitioners across the world. It was estimated that the assay might have at most 30%-50% of sensitivity for patients in early stage of the disease, whilst contact history, clinical manifestations, radiology evidences, and lab results including leukopenia and lymphopenia could be confirmatory for these nucleic-acid-negative pneumonia patients. In the Chinese guideline, patients meeting these criteria were considered as with clinically confirmed COVID-19. In this trial, 46.55% patients in Favipiravir group and 38.33% in Arbidol group

were nucleic-acid-positive at enrollment. Considering the population incidence of COVID-19 infection at the time of this trial in Wuhan, we consider the probability for mis-identifying patients of pneumonia disease other than COVID-19 into this trial is low. Fourthly, the protocol does not prespecify clinical classification as a stratification factor. Ethical concerns arose against completely excluding severe/critical cases from potential beneficial treatment. Additionally, because of the complexity of the disease, progression from moderate to severe/critical is possible. Terminating trial treatment to such patients from the study was considered unacceptable. Post-hoc analysis showed that both treatment and clinical classification contributed significantly to the primary outcome of clinical recovery rate at Day 7. Difference of the frequency of severe/critical patients between groups reached a marginal significance, which made an important impact on the trial outcome.

Previous studies have demonstrated more favourable renal biomarker profiles in TAF-containing regimens compared with TDF-containing regimens; however, the sample sizes of individual trials and the overall low rate of clinically significant renal adverse events in these trials limited the ability to detect differences in the rates of these events with the exception of the pooled pivotal EVG trials. In the present analysis, we integrated data from 26 individual trials and were able to demonstrate the renal safety of TAF over TDF across a broad range of PLH, including those who were treatment naive and those who were virologically suppressed at switch. After 12519 person-years of exposure to TAF, there were no cases of PRT or Fanconi syndrome (identified objectively and independently by the primary investigator caring for the participant) and significantly fewer discontinuations due to renal adverse events in the TAF group compared with the TDF group. Notably, only three (0.02%) renal discontinuation events were reported in participants on TAF; none of these were reported as study drug-related by the investigators, and all had plausible alternative causes.

In treatment-naive participants, we observed fewer overall renal adverse events in participants taking TAF-containing regimens compared with those taking TDF-containing regimens. No difference in overall renal adverse events was observed in participants enrolled in switch studies; this may be explained by the fact that participants in those studies were already maintained on TDF at the time of enrolment, and thus self-selected as less likely to develop renal adverse events.

By using an integrated analysis, we were able to demonstrate favourable changes in renal biomarkers in participants taking TAF-containing regiments compared with those taking TDF, both in treatment-naive and treatment-experienced patients who switched to TAF-containing regimens. Our findings demonstrate favourable changes in CrCl as well as in proximal tubule function (RBP and β2M ratios). We also observed a lower incidence of treatment-emergent proteinuria in participants taking TAF-containing regimens. The observed incidences of proteinuria were high, but notably these are cumulative incidences over 96 weeks of follow-up, and are consistent with previously reported incidences of proteinuria in PLH. These biomarker findings in combination with the clinical outcomes suggest that TAF does not induce proximal tubule dysfunction.

The mechanism for the improved renal safety profile of TAF is likely related to the approximately 90% lower plasma levels of TFV seen in participants receiving TAF compared with those receiving TDF. This mechanism is supported by the reported association between declines in renal tubular function and higher TFV plasma concentrations.

Conversely, the use of boosting agents such as RTV and COBI increase TFV exposure, and accordingly the use of boosting agents has been associated with an increased risk of renal adverse events. A recent meta-analysis sought to compare the renal safety profiles of TDF-containing regimens in the presence and absence of boosting agents, and suggested that unboosted TDF could have a similar renal safety profile as TAF. However, the aforementioned meta-analysis is limited by a relatively small number of participants and short duration of follow-up. In the findings presented here, nine out of 10 PRT cases occurred in participants receiving boosted regimens; however, one severe case of PRT occurred in a participant receiving TDF without a boosting agent. Our data support the principle that boosting agents increase the risk of TFV-associated renal adverse events; however, our ability to make robust conclusions about the renal safety of unboosted TDF is limited by the comparatively small number of participants taking such regimens (of 9322 total participants, 2962 were on TDF, and of those 1101 were on TDF without a boosting agent). Although the question of renal safety of TDF in unboosted regimens warrants more evaluation, the available data indicate that TAF can be safely used with boosted as well as unboosted third agents with a very low incidence of clinically significant renal events.

We note several limitations to our analyses. It is challenging to diagnose PRT, and no commonly accepted single diagnostic exists in the clinic to confirm PRT. As such, we utilized investigator-reported events to document PRT,

which may have underestimated the number of PRT cases. A reporting bias is possible given the use of investigator reported events, but is unlikely to have affected our findings as most of the included trials were double-blinded, and the majority of reported renal discontinuation events and PRT cases were reported during blinded trial phases. Our clinical trial participants may have been healthier than the general population of PLH due to the presence of inclusion and exclusion criteria in the trials, although TAF was found to safe in patients with impaired renal function (CrCl 30–70 ml/min, many of whom with diabetes mellitus, hypertension, and proteinuria), with no reported cases of PRT and overall stable renal function through 96 weeks of follow-up. We also acknowledge that we did not have individual level data on the duration of prior TDF therapy in our trials and therefore could not adjust the rates accordingly.

Despite these limitations, the integrated analysis presented here is based on the large cumulative exposure in person-years to TAF, both in antiretroviral naïve and virally suppressed populations. Furthermore, the pooled data used for analysis includes a demographically diverse population with a wide age range, a large number of women, and diverse ethnic background. It is also notable that a proportion of participants had relatively low CrCl, with variable CrCl eligibility cut-offs of 30, 50, or 70 ml/min in the trials included in this analysis. The clinical trial data are supported by experience from the post approval use in PLH in which currently there has been no renal safety signal with 1.1 million cumulative person-years exposure to TAF.

In conclusion, the pooled data from clinical studies, representing over 12 500 patient-years of follow-up in children and adults on TAF, suggests that the favourable renal biomarker profile observed with TAF vs. TDF in the individual trials translates into a lower rate of clinically significant renal events. These data support a comparative renal safety advantage of TAF over TDF in a broad range of PLH.

In this study of US-based clinical trials with human participants that were published in high-impact journals in 2017, only 15% of the trials could have been feasibly pursued using currently available realworld data from structured EHRs and insurance claims. In particular, replication of the trials of FDA-regulated pharmaceutical interventions was often precluded by the lack of FDA approval at the time of trial publication. Regardless, our estimate was likely a best-case estimate; additional work would be needed to ultimately establish the reliability of observational data sources to generate RWE that could be sufficiently consistent with the trial's intent. Because most trials published in the highest-impact journals were of new drugs that had not yet been approved by the FDA, the findings may reflect that these journals are more likely to publish the pivotal trials that support a new FDA approval.

However, the findings also reinforce the caution about the promise of RWE replacing RCTs. Using observational methods and data sources is not feasible for examining the safety and efficacy of a medical product that is not in widespread use in routine clinical practice.

This study also raises a second caution about the promise of RWE augmenting RCTs. Many of the trials could not be replicated because they would require data that are unlikely to appear in an EHR in structured form if at all. Several improvements in the collection and analysis of EHR data may enhance the use of real-world data to generate RWE, including increased use of patient-reported outcomes as part of routine clinical care, more widespread use of medical device surveillance initiatives, and improvements in natural language processing for free text in EHRs.

The pharmaceutical industry spent $22.4 billion on phase 3 and phase 4 clinical trials in 2011,16 and the total cost of research and development for a single drug has been estimated at $2.9 billion.17 Thus, the theoretical potential for financial savings through RWE-based medical product evaluations is substantial. Furthermore, the evidentiary gaps and unanswered clinical questions that exist are unlikely to be pursued through clinical trials, but for which RWE may offer critical insights. For instance, RWE could be generated as post approval evidence of medical product safety and efficacy for drugs with limited evidence to support their use.18 Similarly, producing sufficient evidence to support an FDA action to communicate a safety concern to patients and clinicians can take more than 4 years.19 Real-world evidence can be used to more rapidly generate actionable safety evidence, which is rarely pursued through clinical trials. Furthermore, RWE may be particularly useful because prospective post approval studies can be difficult to recruit for given that patients can receive the therapy outside the trial, as occurred with the off-label use of atrial septal closure devices.

The FDA continues to invest in its ability to use RWE. As part of the President's Budget for fiscal year 2019, the FDA developed a $100 million proposal to build a medical data enterprise system using EHR data from about 10 million people to build a foundation for more robust postmarketing studies. This investment represents an evolution for the FDA from primarily relying on insurance claims for postmarketing research to using EHR data, which are a

richer source of real-world clinical data and have a shorter reporting lag time than claims data. The proposal also aims to address the lack of standardization of structured EHR data and of interoperability between different systems. In addition, the RWE program of the FDA will develop a framework for evaluating studies that use RWE in terms of the reliability of real-world data sources and the ability of study designs and conducts to meet regulatory requirements. These initiatives could present uses for real-world data that may not have been considered otherwise.

Limitations

This study has several limitations. First, the results are limited to a subset of all clinical trials published in 1 year, although we suspect that these trials represent those that have great implications for clinical practice and that are relevant to clinical practice guidelines and regulators. Second, in establishing whether an intervention could be ascertained from real-world data, we assumed that a pivotal trial for a new indication of a previously FDA-approved drug was replicable because it could theoretically be used off-label, although we did not confirm how common this practice was for each drug and indication. Third, in the analysis of study inclusion and exclusion criteria, we included trials if 80% of the individual criteria were considered as able to be ascertained from structured EHR or claims data, but we did not consider the relative importance or quality of each criterion. Fourth, we considered only primary end points mentioned in the article abstract and thus did not consider all measured study end points, limiting the generalizability of our findings. Fifth, we assumed that an EHR or claims diagnosis would be equivalent to a diagnosis in a clinical trial, which may not always be true given that clinical trials often follow stricter guidelines for diagnosis. For example, in a clinical trial, a diagnosis of myocardial infarction may require specific symptoms and troponin-level patterns, which were not evaluated for feasibility to be ascertained unless they were explicitly stated in the inclusion and exclusion criteria.

In addition, the definition of the feasibility of a trial's characteristics to be ascertained from observational data does not consider whether an observational database would have a sufficient sample with which to perform an analysis (eg, a newly marketed drug or drug for a rare disease) or whether a financial incentive exists to use observational data to replicate a particular clinical trial. Thus, a trial that we identified to be replicable with real-world data may be only suitable to assess sample size feasibility within a given observational data source and then may be found not to be sufficiently powered or feasible to replicate. In addition, the determination of replicability inherently involved an element of subjectivity and did not consider natural language processing as a mechanism for extracting and analyzing real-world data. Although this method has been used in single-center studies, to our knowledge, it is not yet widely applied across health systems for the purpose of generating RWE. As methods become more advanced, opportunities to generate RWE and thereby use RWE to replicate trials will increase.

This study did not consider that the clinical settings in which real-world data are collected are often not the same as the environments in which RCTs are conducted. For instance, patient age, sex, race/ethnicity, or socioeconomic background; clinician location (eg, tertiary center vs private practice); or practice volume are likely to vary between the 2 settings. Nevertheless, this difference is one potential advantage of real-world data because the populations studied are more likely to be representative of the broader population of patients with disease.

In COLCOT, the risk of the primary composite efficacy end point of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization, as assessed in a time-to-event analysis, was significantly lower among the patients who were randomly assigned to receive 0.5 mg of colchicine once daily than among those who received placebo. This result was due predominantly to a lower incidence of strokes and urgent hospitalizations for angina leading to coronary revascularization.

These results were observed against a background of appropriate medications, which included aspirin, a different antiplatelet agent, and a statin in 98 to 99% of the patients. In addition, percutaneous coronary intervention was performed in 93% of the patients for their index myocardial infarction. The benefits of colchicine with regard to cardiovascular end points in COLCOT were at least as large as those of canakinumab in CANTOS.[2] In the small subgroup of patients with available data, as expected, a large (>65%) reduction in the C-reactive protein level occurred over the first 6 months after myocardial infarction in both trial groups in COLCOT, but the difference between the changes in the groups was not significant. These findings must be interpreted cautiously given that this was a small subgroup that was not randomly selected from the full trial sample. A similar observation was made with white-cell counts. The different patient populations involved in the two trials — early after myocardial infarction in COLCOT and stable coronary disease in CANTOS — may also have affected the relationship between biomarkers of inflammation and the effects of treatments on ischemic end points.

The known benefits of colchicine in the treatment of pericarditis were not at play in COLCOT. Postinfarction pericarditis typically occurs within the first few days after the injury, whereas the mean time from the index myocardial infarction to randomization was 13.5 days. There were only two patients with a first positively adjudicated event of urgent hospitalization for angina leading to coronary revascularization within 14 days after randomization, and the median time to this clinical end point was 258 days.

The most common adverse events observed were gastrointestinal. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group, and nausea occurred in 1.8% and 1.0%, respectively. Infection as a serious adverse event was more frequent in the colchicine group than in the placebo group (in 2.2% vs. 1.6% of the patients), and pneumonia as a serious adverse event was also more frequent in the colchicine group (0.9% vs. 0.4%). These differences in the incidence of infections could be due to the play of chance or could reflect altered immunologic responses. In contrast to canakinumab, colchicine did not increase the incidence of septic shock in our trial. Infections have previously been described in patients who have attempted suicide by taking an overdose of colchicine. There was no serious adverse event of myopathy linked to colchicine despite the use of statins in 99% of the patients in the trial.

Our trial has certain limitations. The duration of follow-up was relatively short at approximately 23 months. The risks and benefits of longer-term treatment with colchicine were not evaluated. Although the inclusion of 4745 patients was sufficient for the trial to show a significant benefit with regard to the primary composite efficacy end point, a larger trial could have allowed a better assessment of individual end points and subgroups and the risks associated with colchicine. Finally, our results apply only to patients who have recently had a myocardial infarction.

In conclusion, among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower percentage of patients with ischemic cardiovascular events than placebo.

THE CONTRIBUTION OF BIOLOGICALLY DERIVED PRODUCTS TO THE DEVELOPMENT OF NEW MEDICINES

The annual global medicine market is worth about 1.1 trillion US dollars. About 35 percent of these medicines originated directly or indirectly from natural products including: plants (25%), microorganisms (13%) and animals (about 3%): natural-derived products constitute an extremely important resource for global pharmaceutical companies working on the development of new medicines. They are used as: i) a direct source of therapeutic agents, (both as pure drugs and phyto medicines); ii) a source of raw material for development of complex, semi-synthetic drugs; iii) prototypes for design of lead molecules; iv) as taxonomic markers for discovery of new drugs). About one third of the best-selling drugs in the word are natural products or their derivatives. Of the 520 new drugs approved by Food and Drug Administration (FDA) between 1983 and 1994, 39% were natural products or derived from natural products and about 60 - 80% of antibiotics and anti-cancer drugs are derived from natural products. Recently assessed the role of natural products in the drugs approved by the FDA between 1981 and 2014. They found that in this period the FDA approved 1,562 drugs, 64 (4%) were unaltered natural products, 141 (9.1%) were botanical drugs (mixture), 320 (21%) were natural product derivatives and 61 (4%) were synthetic drugs but with natural products pharmacophore.

There are many examples of globally best-selling medicines that originated from natural products – notably from higher plants, microorganism and animals. Some good examples are: i) the anti-cholesterolaemic agent's simvastain, lovastatin, pravastatin and atorvastatin; ii) the anti-hypertensive agents: captopril and enalapril; iii) the immnosuppressive agents cyclosporin A, tacrolimus (FK506) and rampamycin; iv) the antitumoral agents taxol, docetaxel and campothecin; v) the antibiotic and antifungal agents: penicillin, erythromicin, clarithomycin and anphotericin B.

As noted above animals are the source of about 3% of the new drugs approved by the FDA, but many important and best-selling drugs originated from animals, mainly from toxins. Captopril, an angiotensin-converting enzyme (ACE) inhibitor and anti-hypertensive drug was discovered by Brazilian pharmacologist in the venom of the Brazilian viper, . This is discussed in more detail in the next section. Enalapril was later developed using the same mechanism. Other examples of animal-derived drugs are exanatide, a glucagon-like peptide 1 agonist used to treat type 2 diabetes mellitus, which was originally isolated from the gila of the monster lizard, a peptide isolated from Conus magus which is a calcium 2.2 channel blocker used to treat neuropathic pain (for more detail about new drugs derived from animal toxins see: http://zoltantakacs.com/zt/sc/venoms_medical.shtml).

There are some clear advantages to the use of natural products in the process of drug discovery and development. They represent chemical novelties and compared with other sources they can originate lead drug candidate for complex targets. Furthermore, naturally derived constituents possess a chemical diversity unmatched by any synthetic chemical collection; they can possess bi- and tri-dimensional complex structures yet be capable of being absorbed and metabolised in the body. On the other hand, the use of naturally derived molecules as source of new medicines also presents some challenges because of the lack of specific legislation governing access to biological resources in biodiversity-rich countries. It may also be physically difficult to gain access to natural habitats and the processes necessary to isolate, purify and chemically characterise active compounds are costly and time-consuming. Most pharmaceutical companies complain about the difficulty of assaying some natural molecules in modern drug discovery programmes (high throughput screening) compared with synthetic compounds. Finally, is important to emphasise the great structural complexity of natural molecules, which makes it difficult to synthesise analogous lead compounds. Without doubt the global pharmaceutical industry has benefited greatly from biodiversity-rich countries over the last two centuries when it comes to identification of novel therapeutic targets involved in many significant chronic diseases and, particularly, the development of new drugs for the management of certain chronic diseases.

Brazil is the most biodiverse country in the world, with more than 50,000 species of higher plants (20 - 22% of the planetary total), more than 500 species of mammals, about 3,000 species of fish, more than 1,500 species of birds, more than 500 species of amphibians and millions of species of insects and microorganisms (http://www.sibbr.gov.br/areas/?area=biodiversidade). However, to date few innovative products have been developed and marketed in Brazil or abroad from active constituents derived from Brazilian biodiversity. Despite the growing number of scientific articles published internationally by Brazilian scientists on plants over the last 4 decades, we have seen that there is a negative correlation between the number of scientific papers published on Brazilian biodiversity and the number of innovative products derived from the Brazilian biome that are available on the market. I return to this topic later on in this article.

FROM THE DISCOVERY OF BRADYKININ TO THE DEVELOPMENT OF CAPTOPRIL

In 1949, **Rocha** e Silva (1910 – 1983) and Wilson Teixeira Beraldo (1917 – 1998), who were working at the São Paulo State Biological Institute, discovered the peptide bradykinin (BK), a hypotensive agent that stimulate smooth muscles and is released in plasma by the action of venom of the Brazilian viper, Bothrops jararaca or by trypsin. This discovery was first published in the first number of the journal Ciencia e Cultura, from the newly created Brazilian Society for the Advance of Science, which numbered Rocha amongst its founders. In the same year this discovery was published in the American Journal of Physiology and the article became a much-cited classic.

At the beginning of 1960s, then a young physician who had graduated from the University of São Paulo, moved to Ribeirão Preto to begin a PhD in Pharmacology under supervision of Professor Mauricio Rocha e Silva. Professor Rocha e Silva suggested that Sergio continue work with the venom of the Brazilian viper, Bothrops jararaca. Sergio subsequently discovered that the venom of Bothrops jararaca had a very interesting potentiating effect on the contractile action of bradykinin in the guinea pig ileum and on bradykinin-induced hypotension and he and colleagues identified the active substance responsible as bradykinin-potentiating factor (BPF). These results were published in the British Journal of Pharmacology in 1965. Further investigation of BPF was carried out in collaboration with many researchers from the Faculty of Medicine of Ribeiro Preto allowed to isolate and to sequence two active peptides, the pentapeptide BPP5 and the nonapeptide BPP9.

As soon as he finished his doctorate Sergio decided to spend some years as a post-doctoral researcher in London, at the Professor John Vane Laboratory in the Institute of Basic Medical Science at the Royal College of Surgeons of England. Sergio took with him to London a small sample of the purified BPF for which he and his collaborators had already determined the amino acid sequence and suggested that this venom-derived peptide inhibited the enzyme that degrades BK, which was later recognised to be the enzyme that transforms inactive peptide angiotensin I into the potent hypertensive agent angiotensin II in the body. At the time Professor John Vane was studying some of the mechanisms involved in the control of hypertension and asked to assess whether BPF could interfere with ACE. BPF was found to be a strong ACE inhibitor and these new and interesting results encouraged John Vane to assess BPF as a new tool for development of a new drug to treat hypertension. At the time he was a consultant to the Squibb Pharmaceutical Company in New Jersey, USA. Vane suggested that Squibb should continue the pre-clinical and clinical studies of BPF to develop a new therapy to treat high blood pressure. After overcoming many challenges, in particular the need to convert the BPF peptide into a stable peptide for oral administration and develop large-scale method of synthesising this peptide, as well as the need for clinical research, captopril was finally

approved by the FDA in the early 1980s (trade name capoten), allowing the company's first drug to sell one billion dollars. Currently there are about nine ACE inhibitors on the market and together their sales are worth more than 5 billion dollars per annum. In 1982 John Vane was awarded the Nobel Prize for Medicine and Physiology for his contributions to research on the mechanism of action of aspirin and other non-steroidal anti-inflammatory drugs and for the discovery of prostaglandins. Sergio spent many years working at the Vane´s laboratory and co-authored many papers on these fields.

THE RELEVANCE OF BRAZILIAN BIODIVERSITY TO THE DEVELOPMENT OF NEW COSMETICS

Few Brazilian scientists are currently interested in studying the Brazilian biome in order to develop innovative cosmetic products. However, the Brazilian cosmetic market has been growing at a high rate over the last decade, reaching annual sales of about 13 billion US dollars in 2016. There are 2,642 ANVISA-registered companies that sell cosmetics in Brazil. These companies are represented in almost all Brazilian states, except for the state of Roraima.

Amongst the many examples of plants native to Brazil that have been the source of innovative cosmetic products are babacú (Orbignya speciosa), murumuru (Astrocaryum murumuru), bacuri (Platonia insignis), buriti (Mauritia flexuosa), acaí (Euterpe oleracea), umbu and umbu-cajá (Spondias tuberosa). In 2008, through a partnership between Federal University of Santa Catarina, Financiadora de Estudos e Projetos (FINEP) and Natura cosmetic company, our group studied the standardised extract of the leaves of Passiflora alata, a native plant of Brazil. This project allowed Natura company to develop an innovative cosmetic product, named flavonoid of passiflora, that is still commercially available. The data discussed above suggest that scientific research on the Brazilian biome in partnership with the cosmetics industry should be encouraged, with the aim of developing innovative products.

Included Drugs and Jurisdictions

A retrospective analysis of EMA and HTA reports was performed. All drugs conditionally approved between March 2006 (the start date of the CMA scheme) and December 2018 were included. Included HTA organizations were major European HTA jurisdictions that systematically publish full initial HTA reports and reassessment reports on their websites in a language understood by the investigators, being: England + Wales (National Institute for Health and Care Excellence, NICE), France (Haute Autorité de Santé, HAS), the Netherlands (Zorginstituut Nederland, ZIN) and the European Network for Health Technology Assessment (EUnetHTA). HTA reports were retrieved by searching agencies' websites for the drug generic and brand name and were included until June 2019, to allow time for HTA decision-making after drug approval. Vaccines were excluded because HTA organizations assess vaccines differently from other drugs.

Data Extraction

To investigate the role of SOBs in REAs, data was extracted for regulatory evaluations and HTA initial assessments and reassessments. We recorded general characteristics of drugs including drug name, indication, therapeutic category, orphan status at conditional approval, CMA date (European Commission decision), marketing authorization conversion date (if applicable), and whether the drug had undergone accelerated assessment by the EMA. Drug regulatory data on pivotal observational and interventional studies submitted for approval and to fulfil post-approval SOBs were retrieved from the European public assessment reports. The number of pivotal studies evaluated for approval of the drug and the included primary endpoints within these pivotal studies were recorded. Primary endpoints were categorized as surrogate or clinical efficacy endpoints, or safety endpoints based on the information provided by the European public assessment report and on previous literature describing the type of endpoints in pivotal studies for conditionally approved drugs. Considering post-approval studies, all SOBs were extracted from EMA documents following previously published procedures.

The number of SOBs per drug and their original due dates and final submission dates (if applicable) were recorded. The objective of the SOB (addressing, efficacy, safety or other), type of obligation (clinical trial or other) and its status at approval were also recorded. Again, the primary endpoints for those SOBs entailing clinical trials were categorized as surrogate, clinical or safety.

Data on HTA considerations and conclusions regarding relative effectiveness were retrieved from published HTA reports – including initial assessments as well as reassessments – each matching the initial CMA indication. HTA recommendations that were not substantiated by a consideration of the clinical evidence were excluded (eg, a negative recommendation because no dossier was submitted by the manufacturer). When the CMA concerned

multiple indications that were considered separately by HTA organizations, all were included independently. The same approach was applied when HTA organizations split a single indication into recommendations for 2 or more subpopulations. From HTA reports, the dates of the initial assessment and reassessments were recorded, as well as the outcome of the REA and whether the assessments included a discussion of the (lack of) results from completed SOBs.

Data Analysis

First, descriptive statistics were used to describe drug, pivotal study and SOB characteristics.

Second, based on the dates of included HTA reports, SOB results were categorized as being available for HTA organizations (y/n) in initial REAs as well as in reassessments and it was analyzed whether available SOB results were included by HTA organizations. For initial REAs, the proportions of positive and negative recommendations were compared between those REAs including SOB results and those not including SOB results. To that end, the outcomes of the REAs were categorized into lesser effectiveness, equal effectiveness and higher effectiveness compared to jurisdiction-specific alternative treatments, in line with previous work. When REAs did not include SOBs even though they were already available at the time of HTA decision, it was assessed whether the REA process was already ongoing when SOB results became available. If so, these indications were categorized as having no SOBs available yet.

Finally, the contributing role of SOB results was assessed by investigating the initial and reassessment REA reports for those drugs that had initial assessments that did not include results from SOBs while the reassessments did. HTA organizations' major concerns on the clinical evidence were extracted from the reports' summary statements. From the reassessment reports, statements were extracted about SOB results affecting the assessments and/or assessment outcomes by resolving or not resolving any or all of the major concerns. Major concerns were – in line with previous work – classified into categories related to the trial validity, the patient population, comparative effects, and the relevance of the endpoints and the drug's effect size on those endpoints. Possible changes to REA outcomes were assessed based on the REA categories used within each jurisdiction.

This study aimed to investigate if results from regulatorimposed post-approval studies (ie, SOBs) for conditionally approved drugs were used by HTA organizations within REAs and if so, how these studies have affected reassessments.

Our findings indicate that HTA organizations almost always included results of SOBs for conditionally approved drugs in their assessments, if those results were available at the time of assessment. However, these were only available in a minority of cases, because most initial REAs were performed before any results from SOBs were available. Furthermore, because HTA reassessments were relatively uncommon, most results from SOBs that became available after the initial HTA recommendation were not used within any REA.

In those cases where SOB results became available between the initial assessment and a reassessment, they had variable effects on HTA recommendations. In 4 cases (44%), SOB results directly led to reassessment conclusions that were different from the initial REA. A lack of established comparative effects was most often the major concern resolved by SOBs. In each case these concerns were resolved through newly initiated studies rather than continuations or extensions of pivotal trials. Depending on how convincing the effect sizes were in the SOB results in relation to what was hypothesized in the initial REA, the relative benefit was either upgraded or downgraded in the reassessment. In the other 5 cases, SOB results did not change the REA. In 2 cases this was because there were no major concerns to be solved by the SOB and in the other 3 cases the SOB results did not adequately resolve the major concerns from the initial REA. For one of those 3 cases, the reassessment REA outcome was nonetheless different from the initial REA, due to factors independent of the assessed drug or the SOB results.

Implications

The lack of initial REAs that included SOB study results was expected given the sequence and timing of regulatory evaluations and HTAs in the drug lifecycle: most initial REAs are already finished by the time any post-approval study results become available. Current initiatives between the 2 stakeholders regarding data sharing and parallel evaluations will likely further shorten the timing between regulatory evaluations and HTA. To ensure incorporation of relevant post-approval study results in HTA decisions, a more systematic approach to reassessments by HTA organizations could therefore be appropriate. Currently, there is a clear misalignment between both stakeholders regarding post approval processes. Regulators review the CMA annually and aim to ultimately convert the CMA

status to a standard marketing authorization, while HTA reassessments of relative effectiveness are scarce and rarely timed after the moment of conversion to standard marketing authorization.

Our results also indicate that large differences are present in the (re)assessment procedures of the included HTA organizations. HAS aims to evaluate all drugs, while NICE and ZIN have risk-based selection procedures to decide which drugs they will assess. HAS has a procedure for reassessments that dictates reassessments every 5 years, or when new evidence warrants it. However, the reassessments performed by HAS for our cohort of drugs often included only an assessment of the actual benefit (to determine whether the drug should remain on the positive reimbursement list), while no reevaluation of relative effectiveness was performed. Therefore we could not include these reassessments in our analysis. Similarly, NICE can set a date for reassessment during the initial evaluation when this is warranted, or, if no date is set, checks for new evidence every 5 years. Again, for the drugs included in our analysis often NICE screened the evidence and found a reassessment was not necessary. ZIN can reevaluate drugs, and had a reassessment procedure for a selection of (expensive) inpatient drugs from 2006-2014. No systematic reassessment procedure currently exists and reassessments are rare. Reassessments can also be requested by manufacturers, but because many initial REAs are already positive, there may not be many. Indeed, in our study, for most indications for which a reassessment was performed, the initial REA indicated a lack of or little added benefit. There might also be an underreporting of reassessments when REA outcomes remain unchanged. Other factors, for example capacity restraints, may also contribute to the scarcity of reassessments. Further development of targeted reassessment processes – in line with the timing of evidence development and conversion of conditional to standard marketing authorization – for all HTA organizations can facilitate alignment between HTA reassessments and the CMA process of the EMA. Though EUnetHTA assessments for conditionally approved drugs were found to be extremely rare, EU net HTA has evaluated some CMA drugs approved after the inclusion timeframe of this study (eg, polatuzumab vedotin and crizanlizumab). Besides joint assessments, EU net HTA may play an important role in the standardization of reassessment processes throughout Europe. A good starting point may be the EUnetHTA report on the criteria to select and prioritize health technologies for additional evidence generation. Full alignment on reassessment processes is nevertheless unlikely for the near future because reassessments may also be triggered by cost aspects or by revisions to national confidential pricing arrangements or treatment guidelines.

The changes in HTA recommendations as a consequence of the availability of results from SOBs indicate that post approval evidence can be relevant for HTA organizations. However, our study also indicates that in some cases worries about the quality or relevance of SOB results limited their impact. Lack of study quality or inadequacies in the patient populations, comparators or endpoints have been shown to result in evidence not being helpful for the assessment of relative effectiveness. Previous studies have also highlighted that data requirements from HTA organizations often go beyond requests made by the EMA. Early agreement between regulators and HTA organizations regarding appropriate post-approval study requests could lead to study results that are more helpful for HTA organizations. It has already been shown that regulators and HTA organizations can agree on the most appropriate characteristics for preapproval studies. Possibly, a similar coordinated approach throughout the entire drug lifecycle could facilitate post approval evidence generation. However, firm conclusions about the potential impact of post-approval study results are impossible due to the small number of HTA reassessments. The adequate and timely completion of post-approval studies can be another area for coordination. Research has shown that SOBs are often delayed, changed, or not finished at all. Coordination between regulators and HTA organizations regarding timing and content of (re)evaluations could provide incentives for timely finishing SOBs. Such coordination requires HTA organizations to be free to vary their timing of reassessments.

This study focused solely on REAs, but HTA organizations have repeatedly emphasized that the limited evidence associated with conditionally approved drugs does not justify their high prices.29,30 Post-approval studies could influence the cost-effectiveness estimate as well as the uncertainty in that estimate by providing more information regarding the drug's relative effects. Indeed, the availability of more long term results within the crizotinib reassessment of NICE together with a renegotiation of the drug price led to the overall reimbursement recommendation going from negative to positive, even though the REA had been positive from the beginning. Already, many HTA organizations individually experiment with conditional financing schemes, but the results are mixed and their implementation is uncoordinated across countries.31 European coordination between regulators and HTA organizations could result in a joint definition of the necessary evidence to turn a conditional approval and conditional, limited reimbursement into a standard approval and full reimbursement.

Study design and sample

We used the Drugs@FDA database to identify all novel drugs approved by the FDA between 1 January 2005 and 31 December 2012 on the basis of either a single pivotal trial or pivotal trials focused on surrogate markers of disease, as described in previous work.3 Our sample included all new drug and biologic licensing applications for small molecule and biologic drugs, excluding generic drugs, reformulations, combination treatments of non-novel agents, and non-treatment agents such as diagnostic and contrast agents. Pivotal trials were those labeled as such in the FDA medical review. If the FDA review did not specify, we identified trials that were described as essential to approval, were otherwise prioritized in the review, or were new efficacy based trials provided as part of a resubmitted application for approval.

We also used the Drugs@FDA database to obtain the year of approval for each novel drug and whether it was considered a pharmacologic (small molecule) or biologic product. We used FDA approval letters, which are hyperlinked in the Drugs@FDA database, to identify orphan drugs, drugs approved through the accelerated approval pathway, and the indication for which all novel drugs were initially approved. Orphan drugs were those classified as such by the FDA, meaning drugs for rare diseases that were given extended market exclusivity. The Drugs@FDA database only indicates orphan status for biologics approved after 2010.

Indications were categorized by expected length of treatment using a previously developed framework:3 expected length of use of less than one month was acute, between one month and two years was intermediate, and more than two years was chronic. We used the World Health Organization's anatomic therapeutic classification system, contextualized for clinical relevance, to categorize each indication into therapeutic areas,16 which we collapsed into four categories: cancer, cardiovascular disease and diabetes mellitus, infectious disease, and other.

Systematic review of post approval trials

Two investigators (AMP, JAA) systematically searched all fields of Medline for the international non-proprietary name of each drug to identify all post approval prospective studies in humans that used an active or placebo control and examined efficacy for the same indication for which the drug was first approved by the FDA. We searched for studies published between 1 January of the year before the drug was approved and 31 December 2014. This timeframe was chosen to find studies that started enrolling before FDA approval but did not produce data soon enough to be included in the FDA submission.

Although Medline is not a complete repository of all publications in all biomedical journals, it is the largest database of biomedical journal articles that can be searched freely using the PubMed system. Nearly all doctors and policy makers depend on it to learn about and obtain access to the findings of clinical trials.

Indications approved on the basis of surrogate markers We performed systematic reviews of the literature for all 49 indications for the 48 drugs that were approved by the FDA on the basis of multiple pivotal trials evaluating surrogate markers of disease. We identified a total of 554 published post approval controlled studies using an active or placebo control and examining efficacy for the same therapeutic indication for which the drug was first approved (table 2). Of these, 89.0% (n=493) were randomized, 51.8% (n=287) used open label allocation, 92.4% (n=512) used primary efficacy endpoints that were surrogate markers of disease, 65.9% (n=365) used an active drug as control, 88.8% (n=492) used a superiority design, and 60.8% (n=337) were funded by industry. The median overall intention to treat population was 127 (interquartile range 49-429), and median study duration was 24 weeks (8-48). Among the 325 superiority studies using active comparators, two of eight (25.0%) studies examining clinical efficacy endpoints reported positive results, whereas 143 of 317 (45.1%) of those examining surrogate markers reported positive results (table 3). Among the 139 superiority studies using placebo comparators, 50.0% (two of four) of clinical endpoint studies and 80.0% (108 of 135) of surrogate marker studies reported positive results.

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We aggregated studies by indication and found that the median number of post approval studies for each indication was 3 (interquartile range 1-8) (see supplementary appendix figure 1b), and the median number of randomized and double blind studies was 1 (0-3.5) (table 4). The median number of patients enrolled was 533 (122-3633), and the median number of patients in the intervention arm was 352 (104-2080) (see supplementary appendix figure 2b). The median number of patient years was 448.5 (23.1-2952.0), and the median number of intervention patient years was 350.0 (12.2-1412.8) (see supplementary appendix figure 3b). No post approval studies were identified for eight of 49 (16.3%) approved indications. Twenty eight indications (57.1%) had one or more post approval, randomized controlled, double blind positive study showing superior efficacy, one of which (2.0%) used a clinical outcome for the primary endpoint.

Indications Approved On The Basis Of A Single Pivotal Trial Evaluating Surrogate Markers

We performed systematic reviews of the literature for all 41 indications for the 40 drugs that were approved by the FDA on the basis of a single pivotal trial evaluating surrogate markers of disease. We identified a total of 127 published post approval controlled studies using an active or placebo control and examining efficacy for the supplementary appendix figure 3c). No post approval studies were identified for 20 of 41 (48.8%) approved indications. Six indications (14.6%) had one or more post approval, randomized controlled, double blind positive study showing superior efficacy, two of which (4.9%) used a clinical outcome for the primary endpoint.

We found substantial variation in the quantity and quality of studies of novel drugs published after they were approved by the FDA on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease, or both. We found few published randomized controlled, double blind studies showing superior efficacy based on clinical outcomes that examined the same indication for which the drug was first approved by the FDA after a median follow-up of 5.5 years. These findings have important implications for clinical care. Both doctors and patients have high expectations for the safety and efficacy of a drug approved by the FDA. But less than one third of new drug indications approved by the FDA on the basis of a single pivotal trial had at least one post approval trial showing superior efficacy; even fewer used clinical outcomes. Similarly, less than one 10th of new drug indications approved by the FDA on the basis of surrogate markers of disease had at least one post approval trial validating the use of the surrogate marker by showing superior efficacy using clinical outcomes. Our work corresponds with a previous study demonstrating that highly cited studies are infrequently followed by subsequent clinical studies that confirm original effects and is consistent with a study showing that cancer drugs approved on the basis of surrogate markers are infrequently followed by clinical studies demonstrating improved overall survival.

As well as finding few robustly designed, confirmatory studies, we also found noticeable variability in the degree to which novel drugs were studied in the post approval period, both within and between the categories of approval. Although a small number of approved indications had dozens of qualifying post approval studies, more than one third had no published post approval controlled studies investigating efficacy. Furthermore, across approval categories, the studies showed statistically significant differences in all features of trial design, except randomization, as well as in aggregated median numbers of studies and in patient enrollment.

For many novel drugs, the problem is not that post approval studies are poorly designed or have negative efficacy results, but rather that they are not being published or performed at all. Our findings are consistent with previous studies showing that even post approval studies required by the FDA to be conducted by manufacturers are not always performed in a timely manner and with previous work demonstrating the variability in the number and completion of post marketing studies of high risk medical devices.

The majority of the post approval studies that we identified focused on surrogate markers of disease. Using surrogate markers instead of clinical outcomes for trial endpoints has become increasingly controversial, with several approved drugs ultimately failing to confirm any clinical benefit and an analysis of oncology surrogate markers finding variable correlation with overall survival. Surrogate markers have been used for pivotal clinical studies to facilitate more rapid regulatory evaluation, with the expectation that subsequent clinical studies will focus on clinical outcomes. We found that this occurs infrequently, as approximately 90% of post approval studies of drugs for indications approved on the basis of surrogate markers also used surrogate markers of disease for trial endpoints.

Recent proposals for FDA reform include creating a comprehensive benefit and risk assessment and management plan to be updated at regular intervals and with any shift in a drug's benefit to risk profile7 ; increasing reliance on surrogate markers, smaller and shorter trials, and evidence derived from registries and observational studies ; and switching to a "consumer reports" approach of grades for efficacy, safety, and degree of evidence. Our findings show that caution would be needed for these approaches—high quality post approval evidence does not necessarily accumulate and may require additional regulatory requirements. To strengthen lifecycle evaluation of recently approved drugs, requirements for post approval studies might need to be heightened or might need to specify study design characteristics or trial endpoints in detail to ensure that these studies provide high quality evidence to further inform clinical practice. Of course, it must be remembered that publishing one short term, small post approval study might be inadequate for a hypertension drug but entirely reasonable for one treating a rare disease. A customized, specific plan for post approval studies will be key to generating an adequate amount of post approval evidence on comparative efficacy, which should take into consideration disease prevalence and severity, the drug's anticipated length of use, and the availability of other treatment options.

CONCLUSIONS

Trials are usually powered to detect benefit and seldom designed with adverse events as primary outcome. It is not possible to design trials to evaluate unexpected or unknown adverse effects that have yet to be linked to the intervention. Clinical trials should include explicit pre specified monitoring of pharmacologically predictable adverse events and ensure adequate follow-up of withdrawn participants. Recent regulatory guidance from the FDA has limited the reporting of adverse events in clinical trials from sponsors to those that are unexpected and considered related to the drug. It is unclear how isolated investigators will determine the causal relationship between a drug and its adverse events. The expanding role of electronic trials registers with detailed study results has potential that can only be fully realized when sponsors provide reliable, accurate and complete dat. Empirical work is needed to evaluate whether novel approaches such as mechanism-based drug toxicity prediction can complement safety data from clinical trials and improve an assessment of drug safety. Methodological research is needed to determine whether network meta-analysis techniques can provide reliable and valid comparative evaluation of drug safety. The European Medicines Agency has recently undertaken methodological work to enhance the consistency and transparency of their risk-benefit decision-making process. Current proposals emphasize the need to not just consider the magnitude and consequences of treatment effects, but also to evaluate less tangible factors such as the level of uncertainty and extent of risk tolerance. These developments are particularly relevant when considering rare but serious adverse events where the clinical trials may yield imprecise or even conflicting estimates. Multi-criteria decision analytical techniques that accurately capture quantitative inputs and qualitative values from various stakeholders for risk-benefit trade-offs and allow for quantitative analysis and modelling uncertainty on a range of outcomes can improve complex regulatory decisions about drug safety.

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