BIOMEDICAL POLICY

Scientific considerations for global drug development

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Requiring regional or in-country confirmatory clinical trials before approval of drugs already approved elsewhere delays access to medicines in low- and middle-income countries and raises drug costs. Here, we discuss the scientific and technological advances that may reduce the need for in-country or in-region clinical trials for drugs approved in other countries and limitations of these advances that could necessitate in-region clinical studies.

INTRODUCTION

Making established and new drugs accessible as early as possible to patients in regulatory, resource-limited settings is an important public health issue. Currently, it is not uncommon for countries to require that efficacy or bioequivalence studies be performed in-country before proceeding to marketing authorization, generally delaying the availability of these products by years. The requirement for in-country clinical trials of treatments already approved in other countries can sometimes be scientifically justified. However, these requirements are often based solely on tradition, legal requirements, or political factors, which may include financial incentives associated with the trial. Frequently, the argument is made that different "ethnic" factors are the reason for this requirement, but within a country, there are many different factors that can affect the pharmacokinetics and pharmacodynamics of a drug. In 1998, the International Council for Harmonisation (ICH) published its first guidelines on this topic, entitled "Ethnic Factors in the Acceptability of Foreign Clinical Data," E5(R1), that included definitions of extrinsic and intrinsic ethnic factors. Clarifications of E5(R1) were published in 2003 and 2005 based on questions raised by drug developers (table S1).

In the E5(R1) guidelines, "extrinsic factors" were defined as "factors associated with the environment and culture in which a person resides," and "intrinsic factors" were defined as "factors that help to define and identify a (genetic or other) subpopulation and may influence the ability to extrapolate clinical data between regions" (or between people in a region). Examples of extrinsic factors included environmental (e.g., climate, sunlight, and pollution) and cultural factors (e.g., socioeconomic factors, diet, medical practice, treatments, and regulatory practices), whereas intrinsic factors were classified as "genetic" and "physiological and pathological conditions." Over the past two decades, there have been marked changes in extrinsic factors worldwide, including regional demographics, availability of health care, new regulatory practices, and changes in local and regional environments. Importantly, advances have been made in understanding the intrinsic and extrinsic factors that underlie drug safety and efficacy. In 2017, the ICH adopted guidance E17, which addresses issues that are specific to the planning and design of confirmatory multiregional clinical trials that can be accepted by regulatory authorities.

Here, we propose how to build on the key objectives of E5(R1) and E17, which are to "minimize duplication of clinical data and facilitate acceptance of relevant foreign clinical data in a new region" and to provide a forum for discussion among stringent and national regulatory authorities (defined by the World Health Organization in a 2017 guidance document) (*1*, *2*). We discuss emerging information on the impact of both intrinsic and extrinsic factors on drug disposition that, when combined with established regional variations in these factors, may reduce the need for duplication of clinical trials.

EXTRINSIC FACTORS

Disease prevalence can be strikingly different across regions, leading to substantial differences in the use of medications. Examples include the extensive use of antimalarial drugs in tropical areas and the increasing use of drugs to treat diabetes in South Asia (*3*, *4*). Before making agents available in a country, any prominent regional variables that affect mechanism of disease and pharmacology in the relevant population should be understood and considered.

In this era of genomics and metagenomics, simple descriptions of infectious diseases no longer describe the complexity of microbial infections. Notably, sequencing technologies have led to a new understanding of the genetic differences among pathogens. Understanding local variation in the pathogenicity of a virus can guide therapy selection and avoid periods of ineffective treatment that cause drug resistance. For instance, the prevalence of hepatitis C virus (HCV) varies globally and is complicated by HCV's high genetic diversity

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(*5*). The regional variation in genotype prevalence and the corresponding therapeutic responsiveness across HCV genotypes underscore the impact of HCV genetic diversity. Worldwide, leishmaniasis, a disease caused by the protozoan parasite *Leishmania*, is complicated by the 20 species pathogenic to humans that manifest as four distinct clinical presentations (*6*). The approved label for the drug miltefosine specifies that the drug is indicated for treatment of only a limited number of *Leishmania* species and that, for any particular species, there may be geographic variation in drug response. Pathogen-specific therapeutic intervention is not limited to HCV and leishmaniasis infections but is common in other diseases such as malaria (*7*), human immunodeficiency virus (HIV) infections (*8*), and tuberculosis (TB) (*9*), underscoring the need to consider the prevalence and response of infectious agents during the approval of drugs in different geographic regions.

Malnutrition remains a major problem in resource-limited countries and has increasingly become a major problem for high-income countries where highly processed foods have become dietary staples. In the past decade, our understanding of the mechanisms of drug-induced nutritional deficiencies has increased dramatically. For example, the occurrence of Wernicke's encephalopathy (associated with vitamin B1 deficiency) among a handful of patients with myelofibrosis in Europe, Canada, and the United States terminated the original clinical development of the drug fedratinib, a Janus kinase inhibitor (*10*). Notable nutrient deficiencies exacerbated by drugs include vitamin B1 and B12 deficiency linked to the use of alcohol and proton pump inhibitors, respectively, and calcium deficiencies caused by drugs to treat cancer. Dietary constituents (determined by socioeconomic status and cultural factors) may also be important. For example, in Nigeria, a maize flour or brown rice flour meal afforded a better glycemic response to the antidiabetic drug chlorpropamide, compared to a cassava flour meal, demonstrating that differences in diet can influence the pharmacokinetics and response to certain drugs (*11*).

High-fat meals are known to influence the bioavailability of certain drugs, but food components can also affect intestinal transporter proteins involved in drug absorption. Some fruit juices inhibit the intestinal absorption transporter OATP2B1 and may reduce drug absorption. Dietary supplements, herbal remedies, and concomitant medications may also affect drug absorption and disposition through induction and inhibition of transporters and enzymes (*12*). The herbal remedy St. John's wort induces expression of drug-metabolizing enzymes, thus altering drug metabolism and thereby affecting drug exposure, efficacy, and safety (*13*). Thus, when conducting clinical trials, dietary factors and concomitant medications should be considered. In some cases, these factors can be investigated in the postmarketing setting and need not delay access to essential medicines.

INTRINSIC FACTORS

Human genetic diversity, as with genetic diversity of pathogens, is responsible for some interregional/intracountry variation in risk of disease, drug safety, and drug response. Genetic diversity in genes that encode proteins involved in drug absorption, distribution, metabolism, and elimination (ADME), such as cytochrome P450 enzymes (CYPs), conjugating enzymes, and transporters, leads to changes in drug exposure that are clinically relevant. Genetic studies, including genome-wide association studies (GWAS), have identified many genes responsible for pharmacological variation that may vary among ethnic populations. A striking example of population-specific variation in allele frequencies is CYP2D6, an enzyme responsible for the metabolism of more than 25% of prescription drugs. With more than 100 distinct alleles that may vary in frequency among populations, this polymorphic enzyme accounts for variation in the conversion of codeine to morphine and the metabolism of antidepressants and many other drugs (*14*). For example, *CYP2D6*4*, a reduced-function allele, is present at allele frequencies as high as 18% in Europeans but <1% in East Asians, including Chinese, Japanese, and Koreans, who instead have a higher allele frequency of *CYP2D6*5*, another reduced-function allele (*14*). CYP2C19, another polymorphic enzyme, is responsible for the metabolism of many drugs, including antidepressants and clopidogrel, an anticlotting agent (*15*). The two most common loss-of-function alleles, *CYP2C19*2* and *CYP2C19*3*, are associated with reduced formation of the active metabolite of clopidogrel and consequently increased risk of cardiovascular events in patients taking the drug (Fig. 1). The gene *ABCG2* encoding breast cancer resistance protein (BCRP), which limits drug absorption through intestinal efflux of drugs, also has a common reduced-function genetic variant (rs2231142; BCRP-Q141K) (*16*). A lower dose of the drug rosuvastatin is recommended for East Asians who have a high allele frequency of the *ABCG2* gene variant that results in greater drug bioavailability (Fig. 1). More than 250 pharmacogenomic GWAS have been conducted and catalogued (table S1). As with drug interactions, studies in individuals carrying genetic polymorphisms can often be performed in the postmarketing setting, recognizing that with population dispersion around the globe, genetic variants are not geographically isolated.

PEDIATRIC POPULATIONS

Drug development for pediatric diseases should be treated with the same principles and rigor as for adult diseases. As approval for most medicines used in children generally follows approval in adults, some of the major factors that affect drug efficacy and toxicity may already be clear. Greater experience in extrapolating from adult to pediatric populations, advances in modeling and simulation strategies, and increased understanding of the physiology of children suggest the possibility of modeling the efficacy and toxicity of a drug approved in adults for a similar indication in children (*17*). However, extrapolating the impact of a drug on growth and development from adults to children remains challenging. Drugs for treating cancers and rare diseases in pediatric populations may be modulated by extrinsic and intrinsic factors (*17*–*19*). In such cases, information about these factors and their prevalence in relevant regions is critical, along with information about changes in gene expression during growth and development that could affect ADME of drugs. Considering the great need for pediatric medications and the challenges of conducting pediatric clinical trials, regional postmarketing surveillance activities may be the best strategy to address these issues.

GENERIC DRUGS

Generic drugs account for nearly 90% of prescriptions dispensed in the United States. By 2021, global spending on generic drugs is expected to increase, mainly in emerging markets, where 4 billion of the world's 7 billion people live. Thus, because of their high usage, generic drugs play a critical role in advancing human health globally.

For many generic drugs, a clinical bioequivalence study in healthy volunteers is required. Sophisticated quantitative methods and computational modeling have recently shown great potential for improving generic

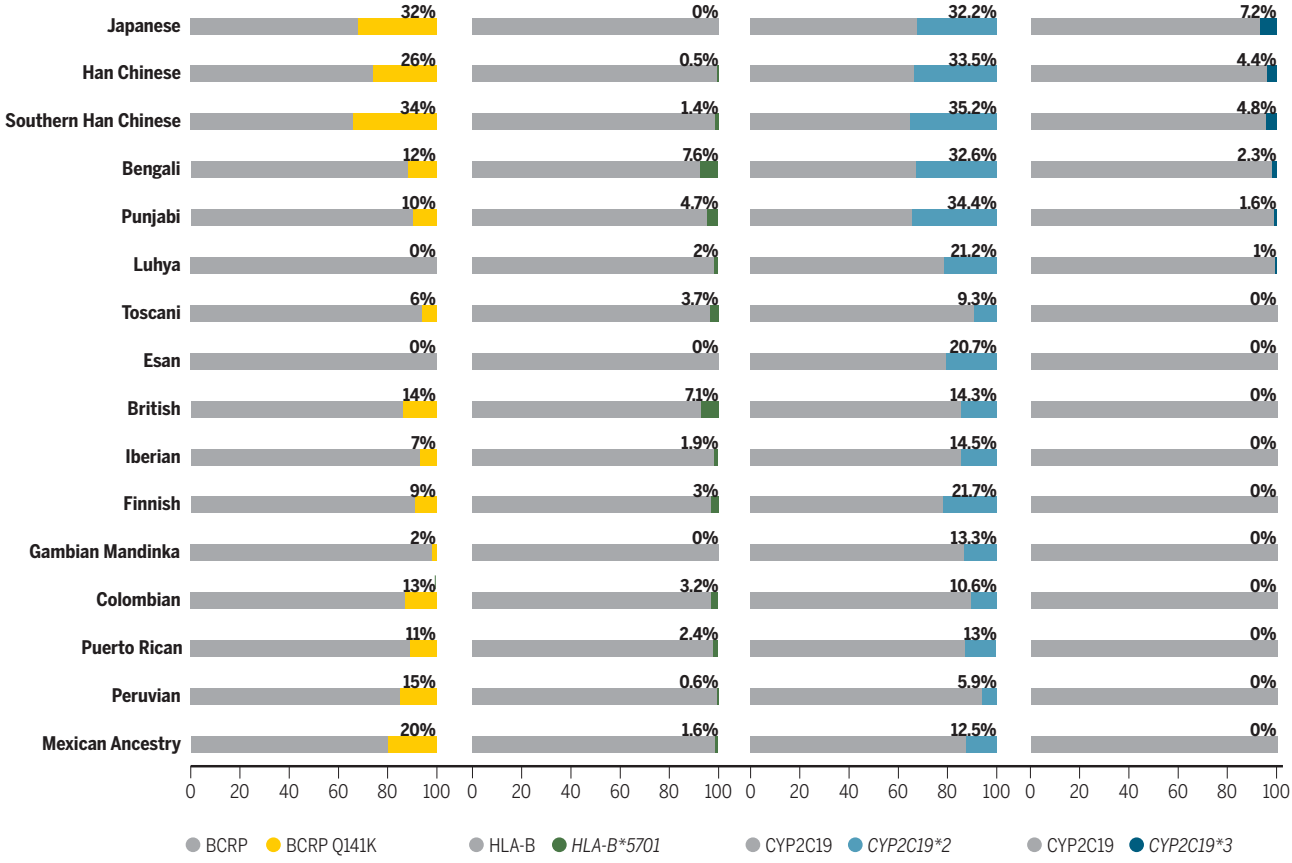

Fig. 1. Genetic differences affect drug responses. Genetic diversity in a selection of genes that encode proteins involved in drug ADME, such as CYPs, conjugating enzymes, and transporters, leads to changes in drug exposure that are clinically relevant. Shown are allele frequencies for selected genetic polymorphisms in 16 different populations that affect drug ADME, including the BCRP-Q141K polymorphism (*ABCG2* gene rs2231142; yellow) that affects bioavailability of the drug rosuvastatin in treated individuals (*16*). Specific human leukocyte antigen (HLA) alleles, such as *HLA-B*5701* (green), are associated with drug toxicities resulting in disorders such as toxic epidermal necrolysis in response to the HIV drug abacavir. The CYP2C19 enzyme has two common alleles that reduce enzyme function: *CYP2C19*2* (light blue) and *CYP2C19*3* (dark blue). These two variants are a major contributor to differences in response to the anticlotting drug clopidogrel, and poor CYP2C19 metabolizers are at increased risk for cardiovascular events when treated with this drug (*15*). Data were exported from the 1000 Genomes website, www.internationalgenome.org, using GRCh38.p13.

drug approval rates by reducing time and cost of product development. In particular, these methods have informed more efficient study designs for comparative bioequivalence evaluation (*20*). Recently, biowaivers for a larger spectrum of products have become available from the European Medicines Agency and the U.S. Food and Drug Administration (FDA). These biowaivers eliminate the requirement for a clinical bioequivalence study for many generic drugs that have excellent absorption characteristics (highly permeable and highly soluble) and for some generic drugs that are poorly permeable but have high solubility. Biowaivers have reduced costs and time for generic drug development and approval. Furthermore, new databases are available to allow for effective formulation of generic drug products (table S1).

Drug formulations intended for the global market should be tested for stability under tropical weather conditions. Because generic drug products have the same active ingredient as the innovator product, intrinsic factors such as genetic polymorphisms are often not relevant to bioequivalence. However, excipients (inactive ingredients that are part of the therapeutic formulation) may differ between brand name and generic drugs, and they may affect the bioequivalence, safety, and efficacy of generic drug products. Although most excipients have a Generally Regarded as Safe (GRAS) designation, there may be intrinsic factor–specific effects of GRAS compounds on various populations. For example, lactose is a common excipient in many medical products, but lactose intolerance is a particular problem for some populations (*21*). Aspartame, a taste-enhancing excipient, affects individuals with phenylketonuria, a genetic disorder that is more common in individuals of Native American or European ancestry (*22*). These issues are usually handled with product labeling. The overall quality of excipients may also vary between regions, and some excipients may be unsafe for use in special populations such as neonates (*22*). In general, dietary and genetic factors should not drive decisions to conduct in-region bioequivalence clinical studies for generic drugs, as those factors would affect the brand name and generic drug product similarly. However, clarification of the excipients that are affected by intrinsic differences is needed.

EMERGING TECHNOLOGIES

Although new technologies have improved our understanding of relevant factors affecting therapeutic responses to drugs, many of these technologies are not available in resource-limited countries where they could have great impact. For example, in vitro technologies

and computational analytical methods can be used to predict drug safety, efficacy, and response for different populations.

These technologies are important for projecting drug effects in low- and middle-income countries. For example, the generation and specific differentiation of human-induced pluripotent stem cells, organoid technologies that mimic three-dimensional tissue structures, and "-omics" approaches such as next-generation sequencing and single-cell RNA sequencing all provide new insights into drug responses. Genome-wide methods have ushered in a new understanding of genes that affect drug responses, but genetic testing is not widely available and reliable in many countries. For example, 20 of 603 international genetic testing laboratories are located in middle-income countries, and none are located in low-income countries (*23*). Gene editing could also play a key role in generating isogenic cell lines for interrogating causal associations between gene mutation–drug pairs.

Computational models, such as physiologically based pharmacokinetic models, can identify potential safety risks. For example, a model incorporating polymorphisms of the *N-acetyltransferase 2* (*NAT2*) gene encoding a drug-metabolizing enzyme, predicted safety and disposition of the TB drug isoniazid, in populations with varying NAT2-metabolizing rates (*24*). This shows that when genetic polymorphisms are known, it is possible to computationally predict how patients will respond to drug treatments (*24*). Intrinsic factors can be incorporated into physiologically based pharmacokinetic models to better predict drug disposition and to study bioequivalence for generic drugs. Further application of these tools, combined with region-specific molecular characterization, could help to inform the necessity of an in-region trial.

Improving clinical trial data collection, quality, and standardization could streamline global clinical trials and downstream interpretation of interregional differences. Infrastructure is particularly important for registered clinical trials that are more common in high-income countries (*25*), and the requirement for in-country trials may create additional challenges. In high-income countries, electronic data captured within electronic health records have the potential to eliminate redundant data entry and improve data quality and processing speed. However, interoperability between electronic health records and the clinical data management system is critical (*26*). Use of electronic health records is still limited in low- and middle-income countries (*27*), and information regarding the handling and reporting of biospecimens lacks standardization (*28*). Large data collections could improve understanding of regional features if these banking approaches are extended to low-resource countries.

Interoperability is further limited by differences in assessment capacity and inconsistent application of ICH principles across national regulatory authorities, especially in low- and middle-income countries. Three areas that would improve decision-making with respect to requiring an in-region clinical trial include (i) increasing the capacity of national regulatory authorities and independent ethics committees or institutional review boards to implement human research ethics in accordance with current best practices worldwide; (ii) increasing the capacity to assess the chemistry, manufacturing, and control of Investigational Medicinal Products in accordance with the ICH common technical document specification; and (iii) expanding capabilities to conduct Good Clinical Practice inspections in line with existing international standards. Efforts in these areas are currently under way through the World Health Organization African Vaccine Regulatory Forum program (table S1).

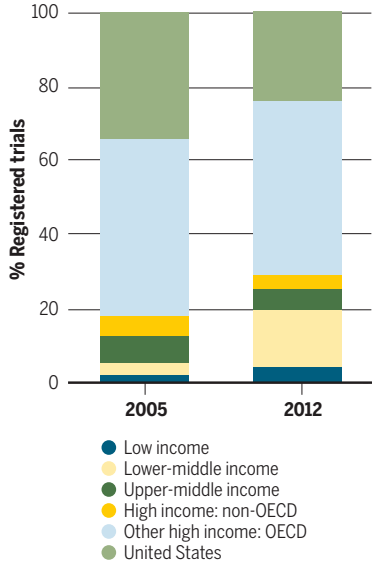

Fig. 2. Percentage of registered clinical trials worldwide. Shown is the percentage of registered clinical trials worldwide in 2005 (left) and 2012 (right) for countries grouped according to income by the Organisation for Economic Cooperation and Development (OECD) (*31*). From 2005 to 2012, the proportion of registered clinical trials in low-income (dark blue) and lower-middle–income (pale yellow) countries increased; the proportion of clinical trials in upper-middle–income countries (dark green), high-income countries (bright yellow), and the United States (pale green) decreased; and the proportion of clinical trials in other high-income countries (pale blue) remained almost the same. Data were extracted from Drain *et al.* (*31*).

Traditional trial designs and statistical analyses of randomized controlled clinical trials are historically challenging and costly. To overcome these challenges, flexible trial designs and statistical methods are being implemented. These include master protocols for platform trials that simultaneously evaluate multiple treatments, Bayesian or meta-analytical methods that derive historical controls by combining historical and study information, Bayesian adaptive procedures that use ongoing observations to refine sample size and trial duration, model-informed and simulation-enhanced procedures, and analysis of real-world data (*29*). For example, Bayesian approaches resulted in ~75% fewer pediatric patients enrolled in a clinical trial of an antidiabetic drug (*30*). A Bayesian approach to evidence generation for drug approval would formally incorporate (prior) evidence of safety and efficacy that has already been accepted by a competent, independent regulatory authority for its approval, together with additional local data if needed. These approaches require intensive planning, often including computer simulations to optimize trial design features, but can be resource-sparing and highly informative.

FUTURE DIRECTIONS

Since the publication of ICH E5(R1) and E17, scientific advances have accelerated the discovery, development, evaluation, and approval of medical products. These advances have refined our understanding of both the intrinsic and extrinsic factors that govern drug disposition, toxicity, and response. Simultaneously, clinical trial infrastructure and methodologies have evolved, and recently, the fraction of registered clinical trials conducted in low- and middle-income countries has increased (Fig. 2) (*31*). This trend, plus inclusion of populations with diverse ancestral backgrounds within individual countries, has increased the representation of different ethnic groups in clinical trials, reducing the need to conduct in-country trials based on intrinsic factors. However, representation of different ethnic groups in clinical trials must be sufficient, and clinical studies need to be appropriately powered to understand the effect of intrinsic factors on the response to and toxicity of the drug under investigation.

At the same time, increased capacity for conducting small, focused, and well-planned pharmacokinetic and safety studies in low- and middle-income countries may be advantageous by providing additional data. Modeling and simulation, including population-based pharmacokinetic-pharmacodynamic and physiologically based pharmacokinetic models, have added valuable capabilities for prediction and extrapolation to specific populations, both within-region and worldwide. Integration of worldwide data from clinical trials and postmarketing surveillance, including data capture methods, is increasingly required by experienced regulatory agencies and the World Health Organization. Using new methodologies and technologies, all countries may wish to incorporate worldwide data in the postmarket setting as a complementary strategy for evaluating in-country drug safety and efficacy. A thorough review of clinical trials worldwide is needed to assess and learn from a number of confirmatory in-country clinical trials. Representatives from stringent and national regulatory authorities should be convened to clarify and prioritize the issues raised by such a review, particularly to identify knowledge and resource gaps that limit the rapid availability of safe and effective treatments for all people, irrespective of the country in which they live.

SUPPLEMENTARY MATERIALS

stm.sciencemag.org/cgi/content/full/12/554/eaax2550/DC1
Table S1. References and websites with information for regulatory sciences.

REFERENCES AND NOTES

1. WHO Prequalification Team: Medicines, *Clarification with Respect to a Stringent Regulatory Organization as Applicable to the Stringent Regulatory Authority (SRA) Guideline* (World Health Organization, 2017).
2. T. F. Blaschke, M. Lumpkin, D. Hartman, The World Health Organization Prequalification Program and Clinical Pharmacology in 2030. *Clin. Pharmacol. Ther.* **107**, 68–71 (2020).
3. N. J. White, Pharmacokinetic and pharmacodynamic considerations in antimalarial dose optimization. *Antimicrob. Agents Chemother.* **57**, 5792–5807 (2013).
4. S. Kalra, A. H. Aamir, A. Raza, A. K. Das, A. K. Azad Khan, D. Shrestha, M. F. Qureshi, M. Fariduddin, M. F. Pathan, F. Jawad, J. Bhattarai, N. Tandon, N. Somasundaram, P. Katulanda, R. Sahay, S. Dhungel, S. Bajaj, S. Chowdhury, S. Ghosh, S. V. Madhu, T. Ahmed, U. Bulughapitiya, Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. *Ind. J. Endocrinol. Metab.* **19**, 577–596 (2015).
5. J. P. Messina, I. Humphreys, A. Flaxman, A. Brown, G. S. Cooke, O. G. Pybus, E. Barnes, Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* **61**, 77–87 (2015).
6. M. Akhoundi, K. Kuhls, A. Cannet, J. Votýpka, P. Marty, P. Delaunay, D. Sereno, A.-L. Bañuls, A historical overview of the classification, evolution, and dispersion of leishmania parasites and sandflies. *PLOS Negl. Trop. Dis.* **10**, e0004349 (2016).
7. A. M. Thu, A. P. Phyo, J. Landier, D. M. Parker, F. H. Nosten, Combating multidrug-resistant *Plasmodium falciparum* malaria. *FEBS J.* **284**, 2569–2578 (2017).
8. C. L. Wallis, C. Godfrey, J. E. Fitzgibbon, J. W. Mellors, Key factors influencing the emergence of human immunodeficiency virus drug resistance in low- and middle-income countries. *J. Infect. Dis.* **216**, S851–S856 (2017).
9. D. Brites, S. Gagneux, The nature and evolution of genomic diversity in the *Mycobacterium tuberculosis* complex. *Adv. Exp. Med. Biol.* **1019**, 1–26 (2017).
10. W. Vainchenker, E. Leroy, L. Gilles, C. Marty, I. Plo, S. N. Constantinescu, JAK inhibitors for the treatment of myeloproliferative neoplasms and other disorders. *F1000Res* **7**, 82 (2018).
11. M. T. Bakare-Odunola, A. Mustapha, I. Abdu Aguye, Effect of Nigerian meals on the pharmacokinetics of chlorpropamide in type II diabetic patients. *Eur. J. Drug Metab. Pharmacokinet.* **33**, 31–35 (2008).
12. J. Yu, Z. Zhou, J. Tay-Sontheimer, R. H. Levy, I. Ragueneau-Majlessi, Intestinal drug interactions mediated by OATPs: A systematic review of preclinical and clinical findings. *J. Pharm. Sci.* **106**, 2312–2325 (2017).
13. S. Chrubasik-Hausmann, J. Vlachojannis, A. J. McLachlan, Understanding drug interactions with St John's wort (*Hypericum perforatum* L.): Impact of hyperforin content. *J. Pharm. Pharmacol.* **71**, 129–138 (2019).
14. K. R. Crews, A. Gaedigk, H. M. Dunnenberger, J. S. Leeder, T. E. Klein, K. E. Caudle, C. E. Haidar, D. D. Shen, J. T. Callaghan, S. Sadhasivam, C. A. Prows, E. D. Kharasch, T. C. Skaar; Clinical Pharmacogenetics Implementation Consortium, Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin. Pharmacol. Ther.* **95**, 376–382 (2014).
15. S. A. Scott, K. Sangkuhl, C. M. Stein, J.-S. Hulot, J. L. Mega, D. M. Roden, T. E. Klein, M. S. Sabatine, J. A. Johnson, A. R. Shuldiner, Clinical pharmacogenetics implementation consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin. Pharmacol. Ther.* **94**, 317–323 (2013).
16. D. J. Brackman, K. M. Giacomini, Reverse translational research of *ABCG2* (BCRP) in human disease and drug response. *Clin. Pharmacol. Ther.* **103**, 233–242 (2018).
17. A. A. Vinks, C. Emoto, T. Fukuda, Modeling and simulation in pediatric drug therapy: Application of pharmacometrics to define the right dose for children. *Clin. Pharmacol. Ther.* **98**, 298–308 (2015).
18. X. Ma, Y. Liu, Y. Liu, L. B. Alexandrov, M. N. Edmonson, C. Gawad, X. Zhou, Y. Li, M. C. Rusch, J. Easton, R. Huether, V. Gonzalez-Pena, M. R. Wilkinson, L. C. Hermida, S. Davis, E. Sioson, S. Pounds, X. Cao, R. E. Ries, Z. Wang, X. Chen, L. Dong, S. J. Diskin, M. A. Smith, J. M. G. Auvil, P. S. Meltzer, C. C. Lau, E. J. Perlman, J. M. Maris, S. Meshinchi, S. P. Hunger, D. S. Gerhard, J. Zhang, Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. *Nature* **555**, 371–376 (2018).
19. J. P. F. Bai, J. S. Barrett, G. J. Burckart, B. Meibohm, H. C. Sachs, L. Yao, Strategic biomarkers for drug development in treating rare diseases and diseases in neonates and infants. *AAPS J.* **15**, 447–454 (2013).
20. L. Fang, M.-J. Kim, Z. Li, Y. Wang, C. E. DiLiberti, J. Au, A. Hooker, M. P. Ducharme, R. Lionberger, L. Zhao, Model-informed drug development and review for generic products: Summary of FDA public workshop. *Clin. Pharmacol. Ther.* **104**, 27–30 (2018).
21. F. Fassio, M. S. Facioni, F. Guagnini, Lactose maldigestion, malabsorption, and intolerance: A comprehensive review with a focus on current management and future perspectives. *Nutrients* **10**, 1599 (2018).
22. K. S. Valeur, H. Holst, K. Allegaert, Excipients in neonatal medicinal products: Never prescribed, commonly administered. *Pharmaceut. Med.* **32**, 251–258 (2018).
23. F. Tekola-Ayele, C. N. Rotimi, Translational genomics in low- and middle-income countries: Opportunities and challenges. *Public Health Genomics* **18**, 242–247 (2015).
24. H. Cordes, C. Thiel, H. E. Aschmann, V. B. A. agents, 2016, A physiologically based pharmacokinetic model of isoniazid and its application in individualizing tuberculosis chemotherapy. *Antimicrob. Agents Chemother.* **60**, 6134–6145 (2016).
25. R. F. Viergever, G. Karam, A. Reis, D. Ghersi, The quality of registration of clinical trials: Still a problem. *PLOS ONE* **9**, e84727 (2014).
26. E. Kellar, S. Bornstein, A. Caban, M. Crouthamel, C. Celingant, P. A. McIntire, C. Johnson, P. Mehta, V. Sikirica, B. Wilson, Optimizing the use of electronic data sources in clinical trials. *Ther. Innov. Regul. Sci.* **51**, 551–567 (2017).
27. S. Higman, V. Dwivedi, A. Nsaghurwe, M. Busiga, H. S. Rulagirwa, D. Smith, C. Wright, S. Nyinondi, E. Nyella, Designing interoperable health information systems using Enterprise Architecture approach in resource-limited countries: A literature review. *Int. J. Health Plann. Manage.* **34**, e85–e99 (2019).
28. H. M. Moore, A. Kelly, S. D. Jewell, L. M. McShane, D. P. Clark, R. Greenspan, P. Hainaut, D. F. Hayes, P. Kim, E. Mansfield, O. Potapova, P. Riegman, Y. Rubinstein, E. Seijo, S. Somiari, P. Watson, H.-U. Weier, C. Zhu, J. Vaught, Biospecimen reporting for improved study quality. *Biopreserv Biobank* **9**, 57–70 (2011).
29. J. J. Park, K. Thorlund, E. J. Mills, Critical concepts in adaptive clinical trials. *Clin. Epidemiol.* **10**, 343–351 (2018).
30. R. A. Huff, J. D. Maca, M. Puri, E. W. Seltzer, Enhancing pediatric clinical trial feasibility through the use of Bayesian statistics. *Pediatric Res.* **82**, 814–821 (2017).
31. P. K. Drain, M. Robine, K. K. Holmes, I. V. Bassett, Global migration of clinical trials. *Nat. Rev. Drug Discov.* **13**, 166–167 (2014).

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