Role of Clinical Pharmacology in Diversity and Inclusion in Global Drug Development: Current Practices and Industry Perspectives: White Paper

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The 2022 United States Food and Drug Administration (US FDA) draft guidance on diversity plan (DP), which will be implemented through the Diversity Action Plans by December 2025, under the 21st Century Cures Act, marks a pivotal effort by the FDA to ensure that registrational studies adequately reflect the target patient populations based on diversity in demographics and baseline characteristics. This white paper represents the culminated efforts of the International Consortium of Quality and Innovation (IQ) Diversity and Inclusion (D&I) Working Group (WG) to assess the implementation of the draft FDA guidance by members of the IQ consortium in the discipline of clinical pharmacology (CP). This article describes current practices in the industry and emphasizes the tools and techniques of quantitative pharmacology that can be applied to support the inclusion of a diverse population during global drug development, to support diversity and inclusion of underrepresented patient populations, in multiregional clinical trials (MRCTs). It outlines strategic and technical recommendations to integrate demographics, including age, sex/gender, race/ethnicity, and comorbidities, in multiregional phase III registrational studies, through the application of quantitative pharmacology. Finally, this article discusses the challenges faced during global drug development, which may otherwise limit the enrollment of a broader, potentially diverse population in registrational trials. Based on the outcomes of the IQ survey that provided the current awareness of diversity planning, it is envisioned that in the future, industry efforts in the inclusion of previously underrepresented populations during global drug development will culminate in drug labels that apply to the intended patient populations at the time of new drug application or biologics license application rather than through post-marketing requirements.

Historically, the demographics of participants in clinical trials have been fairly homogenous with respect to age, race, and ethnicity[1] and may not be associated with the epidemiological disease prevalence. For example, heart failure is reported to be more prevalent in the Black and African American populations (~70%) both globally and within the US. Similarly, sickle cell anemia, although a rare disease, reports a higher prevalence in certain ethnicities, such as Blacks and African Americans, Hispanic Americans from Central and South America, and individuals of Middle Eastern and Asian descent.[2–4] However, this disease prevalence is not reflected in registrational trials of these therapies.[5] This issue has gained attention from lawmakers,[6] regulators,[7–9] and drug developers.[10,11] Of particular note is the recently issued FDA draft guidance on *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials*.[8] This FDA guidance provides recommendations to plan for the enrollment of a sufficient number of participants in phase III studies based on the prevalence of the disease in the target population by race/ethnicity, age, and sex. The guidance also recommends diversifying clinical trials based on additional factors like socioeconomic status, disability, pregnancy status, lactation status, and comorbidities. In the current global drug development paradigm, early patient studies (phase Ib/IIa/IIb) may enroll a relatively small and often homogenous patient population to minimize confounding factors that could otherwise hamper clear assessment of the efficacy and safety of the drug molecule. This homogeneity is because the goal of these early studies is to characterize the preliminary safety, to evaluate the pharmacokinetics (PK)/pharmacodynamics (PD) relationship of the molecule, and to establish proof-of-concept for the molecule in the intended patient population. During these early-stage patient studies, there is limited understanding of the influence of patient characteristics (age,

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sex, race/ethnicity), comorbidities (hypertension (HTN), obesity, organ function insufficiencies, etc.), and any potential genotype differences on the overall safety and efficacy of the molecule. This in turn may limit the enrollment of broader populations during subsequent global, multiregional, phase III/pivotal trials, due to unavailability of sufficient safety/efficacy databases in populations whose baseline characteristics may be outside of the typical demographic distribution. As these pivotal trials are globally conducted, socioeconomic factors, such as the lack of accessibility to healthcare,[12] distrust in clinical trials,[13] operational and technical factors (e.g., single-site studies, cost efficiency, limited sample size, ethical sensitivity, regional availability of standard of care therapies, etc.) may also contribute to the overall underrepresentation of target populations. Downstream effects of these constraints may result in a significant imbalance in enrollment demographics; such socioeconomic factors may widen this imbalance during global development of novel, alternative modalities such as antibody–drug conjugates, mRNA-based therapeutics/vaccines, and chimeric antigen receptors—T that may require enhanced safety monitoring and additional inpatient visits.[14]

As a part of the implementation of the 2022 draft guidance, the FDA recommends that sponsors submit a DP, as soon as feasible during the drug development process, and no later than the End-of-phase II (EoPII). The importance of a DP to regulators is reflected in the passing of "Diverse and Equitable Participation in Clinical Trials (DEPICT) Act" in Congress in December 2022 which goes into effect as a law in December 2025. Implementation of this guidance and planning for trial diversification will require deliberate efforts across multidisciplinary clinical development teams including the field of quantitative pharmacology. Therefore, there is a need to understand how clinical pharmacologists can contribute to these DPs as a part of global drug development.

Thereby, in May 2023, a WG for diversity and inclusion in clinical trials (CT), "D&I in Clinical Trials WG" was formed within the Clinical Pharmacology Leadership Group (CPLG) of the IQ (www.iqconsortium.org). The goals of this WG are to assess the current state of art and opportunities to utilize the tools and concepts of CP in supporting D&I in CT. To this end, the D&I IQ WG, henceforth referred to as "D&I WG" or "WG" throughout this article, has summarized how the discipline of CP could potentially minimize the imbalance in participant demographics and/or baseline characteristics in registrational trials using the following framework:

1. What is the current CP practice in IQ member companies to implement D&I in global CTs?
2. What strategies within CP, can develop confidence in the inclusion of previously underrepresented groups by age, sex/gender, race/ethnicity, and comorbidities in phase III registrational trials?
3. What tools can we use to apply modeling and simulation platforms to inform the variability in drug exposure and to support the safety and efficacy of underrepresented populations?
4. What are the outcomes that will define the success of this initiative? Are there any CP metrics for consideration?

The cumulative efforts and discussions of this WG using the aforementioned framework have been compiled into this white paper. Overall, the scope of this manuscript is as follows:

1. Assess the current state of affairs for DPs in IQ member companies and the role of CP in this regard.
2. Summarize tools based on CP principles to support the enrollment of diverse populations in multiregional clinical trials (MRCT), using model-informed drug development (MIDD).
3. Recommend measures to be taken during all stages of drug development that support the enrollment of broader demographics in pivotal trials (e.g., race/ethnicity, age, sex/gender, and comorbidities) and support trial diversification.
4. Address challenges faced by drug development teams that may preclude enrollment of broader demographics while drafting the DPs.

Although this guidance is focused on drug development and approval of new drugs in the US healthcare system, the general principles discussed in this article are applicable to enrolling diverse populations in global CT.

IQ D&I WG PERSPECTIVES ON CP TOOLS AND APPROACHES TO SUPPORT INCLUSION OF DIVERSE DEMOGRAPHICS IN CLINICAL TRIALS

To explore current knowledge of DPs and utilization of CP principles in drafting DPs, the D&I WG conducted a survey within the IQ member companies. The survey questions were drafted by the WG team members and then reviewed and endorsed by the IQ Board and CPLG. The final survey is composed of 19 questions. The survey and the responses are listed in the Supplemental section. Each IQ member company was requested to provide a single response to the survey, to avoid duplication. The survey was disseminated to member companies by the IQ. Anonymized survey responses were collated by the IQ and shared with the D&I WG. Survey responses were received from 15 IQ member companies, within the consortium. Survey results (Supplement) were analyzed by the IQ WG team members and are summarized here.

The majority of the IQ survey respondents worked in biopharmaceutical companies with > 10,000 employees (**Figure 1a**) and were familiar with the regulatory requirement to submit a DP (**Figure 2a**). Survey respondents were also familiar with the collaborative authoring of these DPs involving cross-functional, multidisciplinary teams that included CP, clinical operations, regulatory, clinical development, and biostatistics (**Figure 1b**). Additional functions contributing to these plans were safety, PK/drug metabolism, epidemiology, and patient advocacy. While the majority of the respondents had submitted at least one DP, in some cases, five or more DPs were submitted to the FDA at the time of the survey response (**Figure 2b,c**). About 20% of respondents did not contribute to DPs because they did not have an opportunity for regulatory correspondence or because their program were in the pre-investigational new drug (pre-IND) to investigational new drug (IND) stages (**Figure 2c**). Overall, the survey demonstrated good awareness of the guidance and its early implementation

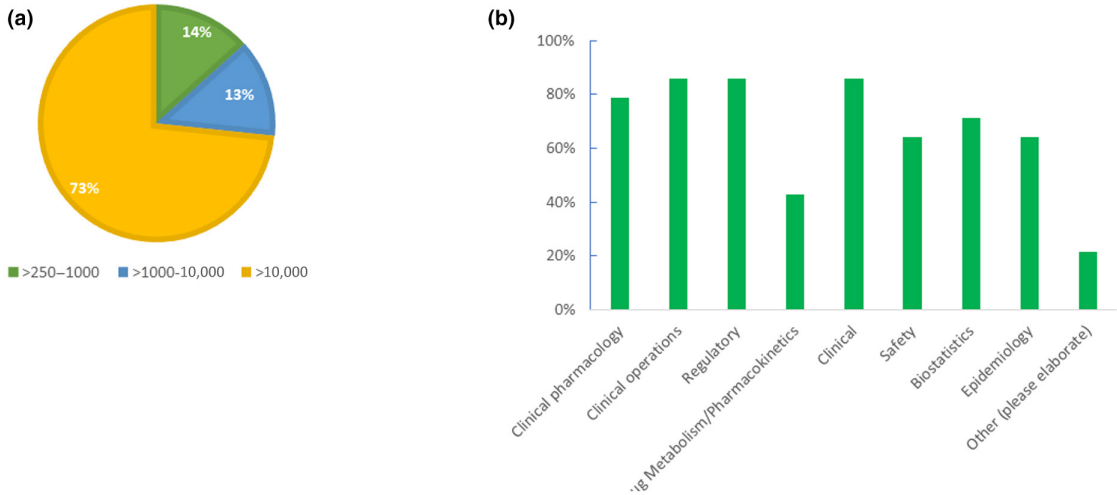

Figure 1 Summary of IQ Survey outputs regarding company size (**a**) and disciplines and functions that contribute to diversity plans (**b**).

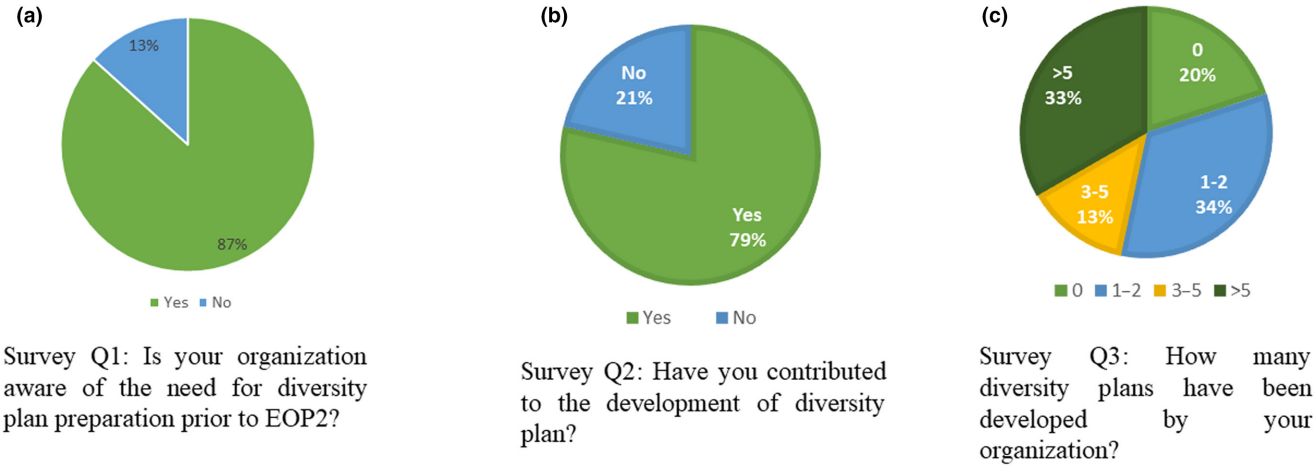

Figure 2 Summary of IQ Survey results on (**a**). Awareness about the need for diversity plan preparation prior to EOP2; (**b**) Contributions or development of diversity plan by survey respondents; (**c**) Number of diversity plans submitted by survey respondents.

within a year of the 2022 FDA draft guidance, among the IQ member companies.

The majority of the DPs were submitted in oncology and cardiovascular/metabolic disease areas. There were only a few DPs submitted in immunology/inflammation, neuroscience, and infectious diseases, and even fewer in cell/gene therapy, rare diseases, vaccines, and device modalities (**Figure 3a**). This pattern may reflect the investments made in these therapeutic areas in the current biopharmaceutical landscape. While the majority of the DPs were submitted after completion of proof-of-concept (POC) studies, either with submission of End-of-phase II (EoPII) background package or at the post-EoPII meeting (**Figure 3b**), the survey responses suggest that in some instances, DPs were submitted with the First-in-human (FIH)/IND application package. An advantage of early DP submission is that it could facilitate dialogue between the sponsor and agency to identify opportunities for data collection and analyses that may be required during early clinical development to support the proposed enrollment goals in global pivotal trials. On the other hand, given the unavailability of clinical data during FIH/IND stages, there may be limited knowledge to support safety and efficacy considerations in a diversified patient population, resulting in substantial modifications and resubmission of the DPs at EoPII.

The survey questionnaire also evaluated the impact of agency feedback on DPs. In most of the survey responses, regulatory feedback on DPs did not result in major revisions to the overall clinical development program, including planned studies, timing of the planned studies, study conduct, and inclusion/exclusion criteria (**Figure 4a,b**). In some cases, agency input resulted in changes to site selection, country selection, or enrollment goals. The survey suggested that respondents received FDA feedback on modifications to enrollment thresholds of demographics such as gender and race/ethnicity. FDA feedback did not result in any impact on the overall timing or sample size of trials. In addition, respondents also received feedback on the removal of protocol exclusion criteria for comorbidities such as HTN and obesity. This was likely suggested with the intent of including racial/ethnic participants that may present a relatively higher prevalence of these comorbidities within

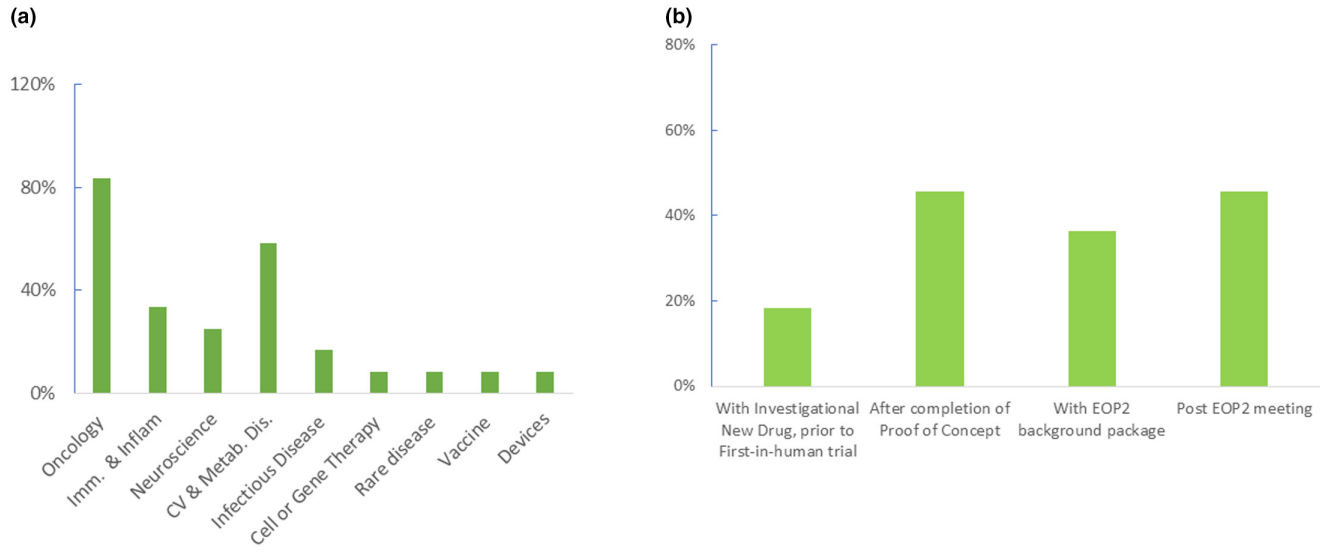

Figure 3 Summary of IQ Survey output on (**a**), the therapeutic areas where diversity plans were developed; and (**b**) Stage gates of agency submission survey respondents.

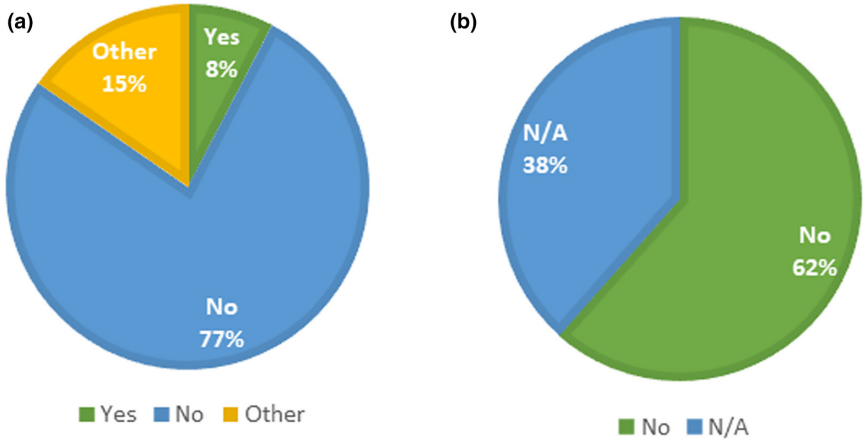

Figure 4 Summary of IQ Survey output on the impact of the FDA review following diversity plan submission on (**a**) timing of planned studies and (**b**) inclusion/exclusion criteria.

the intended patient population. In some instances, additional exposure–response and subgroup analyses for efficacy and/or safety were requested by the agency. The inclusion of populations with comorbidities is likely to mimic the real-world situations in phase III/pivotal trials. For example, in oncology, the most prevalent comorbidities in patients diagnosed with colon cancer, rectal cancer, or lung cancer have been reported to be HTN, chronic obstructive pulmonary disease (COPD), and diabetes mellitus (DM),[15] whereas for breast cancer, comorbidities, such as ischemic heart disease, osteoporosis, hypothyroidism, and DM, ranked high.[16] Similar situations exist in chronic disorders, such as chronic kidney disease (CKD) in which HTN and DM are common comorbidities.[17] These chronic conditions could lead to exclusions during global CT either due to the potential for drug–drug interactions (DDI) in the case of patients taking medications to manage these comorbidities, or due to baseline characteristics which may not meet trial inclusion/exclusion criteria for safety laboratory parameters, vital signs, etc. CP approaches including dedicated CP studies and/or model-based approaches should be evaluated to assess the impact of such comorbidities preferably before EoP2. For example, the extent of renal elimination of drugs determined from phase I/dose escalation studies could inform whether patients with moderate renal insufficiency could be enrolled in phase IIa/IIb studies, which in turn could support dosing decisions for patients with renal insufficiencies during phase III.[18] Adequate safety data collected from renally insufficient patients in phase IIa/IIb may also inform the enrollment of severe, renally impaired patients in phase III trials, especially if renal elimination is not a predominant route of clearance. Similarly, model-based approaches such as physiologically-based pharmacokinetics (PBPK), population-based pharmacokinetics (PopPK), and exposure–response analyses may inform teams about the safety/efficacy and any clinically meaningful dose adjustments necessary in populations predisposed to renal or hepatic insufficiencies[19–21]; similarly employing

these model-based approaches using data from early clinical studies may allow for enrollment of patients in which body weight or body mass index (BMI) may be outside of the typical ranges,[22] or in patients with HTN.[23] Standard protocol criteria pertaining to cardiovascular and metabolic parameters may limit the inclusion of populations in whom these comorbidities are prevalent,[24] potentially leading to the exclusion of racial and ethnic subpopulations which may be predisposed to such cardiometabolic traits.[5] In such cases, sponsors may consider it extending the application of exposure–response analyses conducted using data from early clinical studies. For example, the outputs of concentration-QT (C-QT) analyses[25] conducted after phase I/Ib studies could be applied to assess the safety of comorbid populations with HTN. Such an assessment could allow for the inclusion of racial and ethnic populations with hypertensive comorbidities if the C-QT analyses suggest no drug effect on cardiac parameters and if protocol-specified monitoring plans allow for such inclusion. Applications of C-QT analyses could also inform clinical teams of any required dose modifications, in such patients. Additionally, the use of real-world data (RWD) and epidemiological analyses could inform the overall distribution of baseline parameters of laboratory assessments and vital signs in populations of interest.[24] Similarly, polypharmacy which is inherent in almost all patient populations to a varying extent, could be assessed through the conduct of DDI assessments prior to EoP2 either via dedicated safety run-in periods of global trials or via application of PBPK approaches. These assessments prior to EoP2 could support the safety and efficacy of selected phase II/III dosing in comorbid populations by informing the potential impact of DDIs at the selected dose level and if any dose modifications are needed.

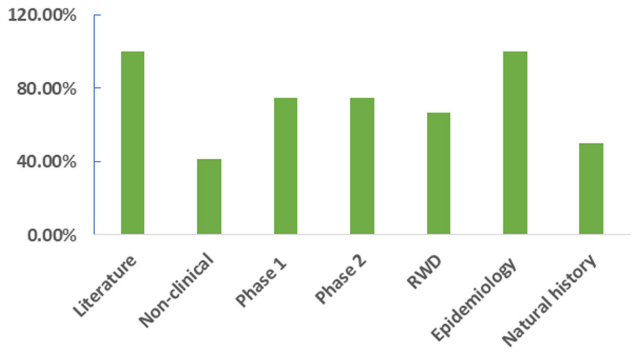

Figure 5 IQ Survey responses on which data informed the development of the DP. Select all that apply.

The IQ survey questionnaire probed the data sources that summarized the contents of the DP. Key sources included literature or epidemiology data and observations from phase I and phase II results (**Figure 5**). Such datasets obtained from methodology studies could be significant for understanding disease prevalence in different populations globally and could inform the key areas of significance for MRCTs. The survey responses also suggested that member companies were using data from ethno-bridging studies, special population PK bridging studies, PK/PD/pharmacogenomic studies (e.g., epidermal growth factor receptor, human leukocyte antigen (HLA) mutations, etc.), DDI studies, and food effect studies (**Figure 6a**) to support DPs. (Note: survey respondents could choose more than one option for this question). According to the survey, the most prevalent modeling and simulation approaches used for drafting DPs were PopPK, PopPK/PD, exposure–response analyses, PBPK analyses, and quantitative systems pharmacology (QSP). Utilization of disease progression modeling and Artificial Intelligence (AI)/Machine learning (ML) approaches to inform DPs ranked relatively low at the time of the survey (**Figure 6b**). With emerging awareness and increasing uptake of AI/ML and disease progression modeling[26] it is anticipated that these approaches will be increasingly applied to integrate patient characteristics in the near future. IQ survey respondents suggested several CP approaches and tools that could develop confidence for the inclusion of previously underrepresented subpopulations. These approaches could be summarized into a couple of distinct themes:

1. MIDD approaches: Respondents provided model-based approaches such as PopPK, exposure–response, subgroup analyses, PK/PD, kinetic-pharmacodynamic models, PBPK, use of

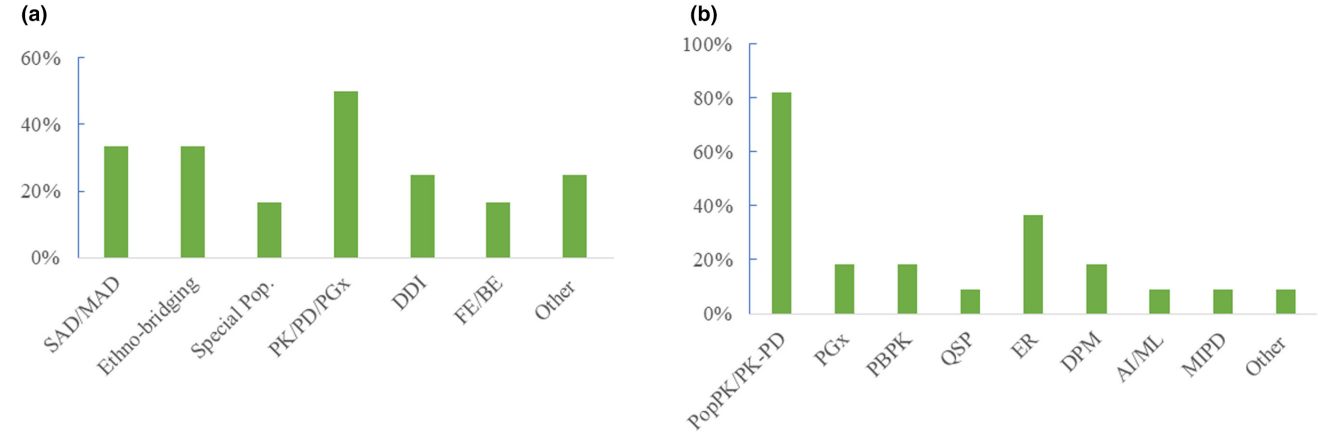

Figure 6 IQ Survey responses on (**a**). Use of clinical pharmacology studies included in diversity plans and (**b**) clinical pharmacology and pharmacometrics analyses that were included in diversity plans.

real-world evidence (RWE)/RWD, and stratification based on pharmacogenomic analyses.
2. CP and operational approaches: Respondents provided approaches, such as conducting ethno-bridging studies, opening metropolitan study sites globally, diversification of phase I studies, early conduct of organ impairment studies, broadening enrollment of populations in phase III, sparse PK sampling in pivotal trials to quantify any signals observed in broader patient populations, utilizing patient-centric sampling techniques, etc. A summary of these approaches is depicted in **Figure 7**.

While the survey also provided a venue to share case studies or examples of DPs, none of the respondents provided such data most likely due to the proprietary nature of information that is included in the DPs.

D&I WG PERSPECTIVES ON CP TOOLS AND APPROACHES TO SUPPORT INCLUSION OF DIFFERENT DEMOGRAPHICS SPECIFIED IN DPS

Race and ethnicity

Enrolling epidemiologically requisite racially/ethnically diverse populations in pivotal trials is one of the key goals of the April 2022 FDA draft guidance. This requires an early understanding of differences in safety, efficacy, and pharmacokinetics of investigational drugs, across racially diverse patient populations, especially in those racial subpopulations in which the disease is highly prevalent. While we may not have clinical data in the early stages (FIH/phase Ib) to evaluate dosing strategies by race/ethnicity, it should be noted that protocol criteria do not restrict the inclusion of participants by race or ethnicity. Over the years, the impact of several factors, such as genetic polymorphism,[27–30] environmental factors,[31] and body weight composition[32] on PK[33] as well as on drug response[28,34–36] have been well understood. It is therefore important to assess the clinical meaningfulness of differences in drug response across race/ethnicities due to these intrinsic and extrinsic factors. A formal assessment could be conducted using dedicated ethno-bridging studies (e.g., to bridge exposures between non-Asian and Asian participants during early drug development[37]). Kelleher *et al*.[38] conducted a single-dose, FIH trial of a combination agent in Japanese healthy participants. A lack of differences in systemic exposures of the individual constituents dosed as monotherapies vs. in combination within the same study supported the inclusion of Japanese participants in the global phase III registrational study. In a recent move to promote the participation of Japan in global, MRCTs during early drug development as well as to facilitate timely inclusion of Japan into global pivotal trials, the Pharmaceuticals and Medical Devices Agency (PMDA) has relaxed existing regulations for dosing of investigational agents in Japanese participants. These regulations allow the use of global safety data to potentially initiate trials without the need for a dedicated phase I study in Japan, if the safety of the investigational agent is deemed acceptable at the dose to be evaluated in MRCTs in Japanese populations.[39] This could immensely benefit global drug development paradigms in which MRCTs could be initiated in Japan using available safety datasets from a global safety database. Initiating such studies in Japan early on could benefit DPs by generating safety data from Japanese participants in real time. For investigational drugs in which the predominant clearance mechanism (> 70%) may be via polymorphically expressed cytochrome P450 (CYP) in compounds with a narrow therapeutic window, prospective collection of genotype status in early clinical studies can be conducted.[40] This could allow for stratification of patients based on their genotype and dose adjustments, if necessary.[41,42] Alternately, discounting such risks in phase Ib/IIa/IIb studies by

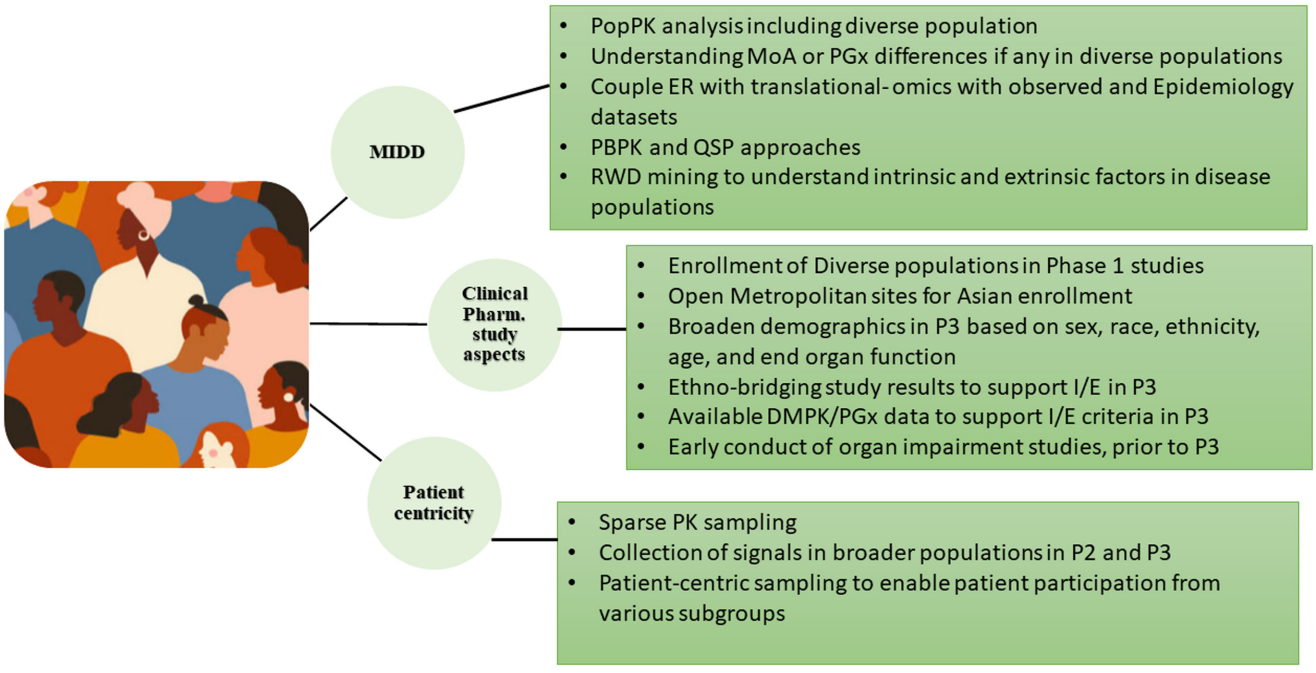

Figure 7 Survey Q16: Open text response from survey respondents on Clinical Pharmacology approaches to improve DEI.

assessing participants of all genotypes could support enrolling all comers in phase III without any need for genetic testing, thereby reducing additional procedures in larger, global phase III trials.[43] It should be noted that such analyses may require adequate knowledge of the fractional dose metabolized by polymorphic enzymes, requiring mass balance/absorption, distribution, metabolism, and excretion studies to be conducted during early clinical development, especially for compounds with a narrow therapeutic window and in which the clearance mechanisms are anticipated to be predominantly via polymorphically expressed CYPs or transporters.[44] Alternately, sensitivity analyses using PBPK model-based assessments may help determine the impact of polymorphic isozymes and dose adjustments, only if necessary.

Since the advancements of MIDD in lieu of dedicated clinical studies, the industry has been using model-based approaches to understand the clinical meaningfulness of racial/ethnic differences using covariate testing via PopPK and exposure–response analyses.[45,46] Fediuk *et al*.,[47] have used model-informed assessments to rule out clinically meaningful differences in ertugliflozin PK, across different Asian ethnicities. PBPK-based tools are also widely accepted across regulatory landscapes globally to predict exposure differences and drug interactions as well as to defer or waive DDI studies across racially diverse subpopulations.[48–50]

Race and ethnicity may be clinically significant covariates of safety, efficacy, or PK, and with or without clinical meaningfulness. If these covariates are clinically meaningful, dose titrations or adjustments may be needed based on racial/ethnic stratifications.[51,52] These dosing strategies may become particularly challenging when the target population shows comorbidities that are highly prevalent in particular races or ethnic groups[53] (e.g., HTN or organ impairment by race/ethnicity). In such cases, teams may consider using global epidemiology databases to understand these comorbidity patterns and assess exposure–response in appropriate subpopulations, as discussed in the previous section. While statistically significant covariates resulting in clinically meaningful exposure–response may lead to dose titrations or adjustments across racial/ethnic populations (e.g., lenvatinib),[51,52] a methodical review suggests that such differences in posology by race/ethnicity have not been very commonly observed in the US and European Union (EU) drug labels.[52]

Based on available data, if no dose adjustment is required across racially/ethnically diverse populations, summarizing this in the DP during regulatory correspondences such as EoP1 and EoP2 [commonly referred to as Recommended phase II dose (RP2D) in oncology] as suggested in the FDA guidance,[8] could result in the successful inclusion of such populations in global phase III trials. Alternately, drug products requiring a dose adjustment based on race/ethnicity may require sponsors to exercise additional caution through an adequate safety monitoring plan to support the enrollment of such subpopulations and minimize their exclusion from global trials.

Age

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance classifies age groups chronologically into neonatal (birth 27 days), infants (28 days–23 months), children (2–11 years), adolescent (12–< 18 years), adults (18–< 65 years), and elderly (≥65 years). CT in the 90s largely enrolled only adults (18–< 65years) at all stages of drug development through first approval. Much progress has been made over the years in reversing this trend for pediatric drug development, since the commencement of initial draft guidance on pediatric drug development as a result of the Pediatric Research Equity Act (PREA), Best Pharmaceuticals for Children Act (BPCA),[54,55] and initial pediatric study plan/pediatric investigation plan (PIP) within the European Medicines Agency (EMA), reducing lag times between first approval for adults and pediatric population. The EMA recommends that all marketing applications for authorization include the results of studies described and agreed upon through PIP unless deferred or waived. Under the "Stepwise PIP" plan, the timing of the PIP should be "not later than upon completion of the human pharmacokinetic studies in adults, i.e., early in the product development," it could be at the time of initiation of phase II studies but cannot be after initiation of pivotal studies.[56] The BPCA particularly incentivized sponsors to conduct pediatric research for up to 6 months' extension of patent and exclusivity. An IQ working group has supported the implementation of these best practice guidance and included a MIDD framework to conduct pediatric extrapolations.[57,58] Recently, there has been increased interest in including adolescents in adult CT to ensure the timely availability of innovative medicines within this age group. Given the importance of developing innovative medicines for adolescent populations to help prevent off-label drug use, health agencies have drafted guidance documents that provide recommendations on the acceptability of including adolescents and older children in adult CT.[59] Several of the key considerations for the inclusion of adolescents in CT are (i) differences in target expression/PD/disease severity between adults and adolescents, (ii) differences in PK,[60] (iii) differences in safety and tolerability,[61] and (iv) logical as well as operational considerations when conducting CT in adolescents.

Clinical pharmacology (CP) plays a key role in informing the optimal dose. Dose selection in adolescents could be conducted using model-based assessments or using a Bayesian approach; whereas emerging clinical trial data from adult populations can inform the likelihood of dose similarity between adults vs. adolescents. Based on analyses by Momper *et al*.,[62] the majority of drug products have shown dose equivalency between adolescent and adult populations at the time of first approval. Similar recommendations have been made in FDA guidance[59] for adolescent enrollment in oncology trials in which up to a lower bound of 40 kg body weight (BW) dose equivalency could be considered if available adult clinical data do not require body weight or BMI-based dose adjustments. Sponsors may also identify a prespecified number of adult patients as enrolled or as completers to initiate the enrollment of the adolescent population in phase IIa/IIb studies using an adaptive trial design. Similar adaptive designs also could be imagined for phase III studies which include elderly populations. Comorbidities in elderly populations are a significant concern due to potential safety concerns. According to the CDC,[63] most prevalent comorbidities in elderly populations are reported to be HTN, cardiometabolic

disorders, inflammation (asthma, arthritis, and COPD), dementia, and depression. As discussed previously, exposure–response assessments for patients with such comorbidities should be considered during data collection and analyses of early CT as well as incorporated routinely into drug development. An IQ WG on elderly populations is currently in progress. Conducting safety run-in arms or nested DDI studies with typically prescribed co-medications such as verapamil and rosuvastatin[64] may support the inclusion of elderly participants in pivotal trials in real time. Similarly, for predominantly renally cleared drugs, conducting renal impairment studies during or in parallel to phase II may be necessary to support the enrollment of elderly populations in global phase III studies. Where opportunities exist, model-based assessments like PBPK or empirical population-based approaches using cumulative data from phase Ib/ IIa/IIb and a risk-based assessment could help dissipate such concerns regarding common comorbidities and enable enrollment of elderly populations in phase III.[65]

Sex/gender

Up until the 1990s, CT were largely enrolling male populations. The formation of the FDA Office of Women's Health initiatives and guidance[66] promoted enrolling women in CT; since then, there has been significant attention toward the inclusion of women in CT. While women of non-childbearing potential can be generally enrolled in trials with minimal safety concerns, women of childbearing potential (WOCBP) are sometimes excluded from clinical studies due to risks associated with potential embryo-fetal exposures of investigational drugs, until embryo-fetal toxicity data (EFD) can support their inclusion (ICH M(3)R2). In some instances, in the absence of EFD studies, sponsors may consider the inclusion of WOCBP in CT with adequate contraception requirements in protocols (at least 2–3 methods of contraception). After completion of EFD studies, WOCBP is enrolled in CT. Oftentimes, these EFD studies are conducted after an adequate understanding of the drug disposition (e.g., mass balance studies and dose optimization activities), once the potential phase III dose has been selected. However, including WOCBP in the early phase and proof-of-concept CT is essential, especially for disorders which disproportionally affect women (e.g., urinary tract infections, Rett's syndrome, polycystic ovarian syndrome, systemic lupus erythematosus, etc.) to minimize delays in recruitment, retention, and approval processes in the main population of interest.

Therefore, for indications with a higher prevalence in women, sponsors may consider conducting EFD studies in parallel to phase I or phase IIa trials to support the inclusion of women of all reproductive capabilities as early as in phase IIb trials. Collecting safety and PK from these mid-stage trials in women of all reproductive abilities could then support their enrollment in global phase III trials. Duration of dosing may also be a key consideration in this regard. The FDA guidance[66] suggests that there is a relatively lower rate of pregnancy (< 0.1%) observed in phase II/III trials where the duration of dosing is limited to 3 months or less and in which sample size is < 150 participants, making such studies suitable in consideration of gender-based health equity. In contrast, the inclusion of WOCBP in CT may need additional considerations for long-acting injectables in which drug properties (i.e., long half-life) and route of administration (subcutaneous or intramuscular) may result in measurable concentrations in systemic circulation for 9 months to a year or longer, following participants' last dose. In such cases, WG recommends conducting EFDs prior to EoP2 to enroll women of all reproductive capabilities in pivotal trials.

With respect to the enrollment of transgender individuals in registrational trials, similar to race/ethnicity, clinical trial protocols do not include any restrictive language on enrollment of transgender individuals. While differences may exist in physiological processes, endocrine functioning, and expression levels of drug-metabolizing enzymes and transporters by gender,[67,68] to date, there are no reports on dose adjustments or clinically meaningful differences in PK, PD, and/or safety/efficacy across transgender vs. male vs. female populations for any of the approved drugs. However, this conclusion is based on a very small dataset available for this comparison. If adequate safety margins permit, WG suggests enrollment of all genders, including the transgender population in pivotal registrational trials. It cannot be ignored that the transgender population may be at an increased risk of comorbidities.[69–71] Therefore, the safety/DDI risks associated with polypharmacy in this population should be thoroughly considered before broadening enrollment. The WG anticipates that in the next few years, we may see an increase in enrollment in such underrepresented populations, and teams will continue to learn about transgender individuals through observational studies and applications of model-based assessments.[72]

RECOMMENDATIONS AND CHALLENGES

Recommendations

1. To implement the DP, sponsors should consider studies and datasets from early development stages more holistically (e.g., learn from outliers as sources of inter-individual variability rather than striving to minimize variability, assess the PK and the safety and efficacy of molecules in patient populations of high disease prevalence based on the epidemiology of the disease, etc.). Teams also should consider the inclusion of the intended patient populations in phase Ib/ IIa/IIb stages in order to assess the impact of covariates prior to EoP2.
2. Teams should determine the distribution of demographics (e.g., age, body weight, BMI, sex/gender, and race/ethnicity) as well as learn about the common comorbidities and co-medications in the intended patient populations. The use of RWD, epidemiology datasets, virtual populations, etc. could assist with identifying the baseline characteristics of these comorbidities. Assessing safety and efficacy differences between extreme bounds of demographic characteristics using fit-for-purpose modeling and simulation (e.g., HTN in Blacks and African Americans, low BMI in Asians, body weight-based dosing, etc.) and considering adequate safety monitoring plans may allow for better representation of such populations in global pivotal trials. Conduct of multivariate analyses should be mainstream to assess safety and efficacy in populations with comorbidities such as HTN, organ impairment, high/ low BMI, etc.
3. Consider the merits of submitting DPs at FIH/ IND/phase IIa stages, if this activity may provide an opportunity to develop an early partnership and dialogue between sponsors and

health authorities to support diversity planning for global trial conduct.

4. Applying results and learnings within subgroups from MRCTs (e.g., safety and tolerability datasets in patients enrolled in Asia, Africa, etc.) to inform DPs as well as extrapolating these learnings to support marketing applications in different countries could reduce the need for unnecessary trials and dedicated substudies. Conversely, assessing comparability of indications/demographics and extrapolating the results of drug development program from first markets (e.g., the US and EU) to the rest of the world could greatly accelerate drug development and access of investigational drugs in emerging markets.
5. During mid to later stages of drug development, sponsors could consider using MIDD paired meetings to provide an assessment of safety and efficacy across broader populations (e.g., flat dosing in all demographics or dose modifications as needed) and to support enrollment of all comers in phase III based on disease prevalence.
6. For populations that may not have access to health care due to socioeconomic circumstances (e.g., unavailability of clinical trial sites within close quarters, disability issues, functional impairment which preclude individuals from making frequent trips to sites), allowing patient-centric measures (e.g., sparse sampling schema, use of digital or at-home collected data to develop exposure–response models, fit-for-purpose PK sampling schemes, PK/PD sampling plans tailored to minimize site visits, development of at-home sampling/bioanalytical methods like volumetric absorptive microsampling (VAMs)[73]) may minimize the time, efforts, and costs associated with traveling to the clinical sites.
7. Adaptive phase 2a/2b study designs to enroll broader populations should be considered. These include participants who may fall outside of typical ranges of age and BMI, and/or patients with comorbidities (e.g., HTN, organ insufficiencies, etc.). Such adaptive designs could take advantage of prespecified safety datasets to inform the dose selection of broader populations during early clinical studies to generate a sufficient safety database for supporting enrollment of such broader populations in global phase III studies.
8. For compounds being developed across multiple indications, diversity goals may change based on the disease prevalence for each indication. The framework of DPs for each molecule will most likely be preserved across indications, except when exposure–response (efficacy and/or safety) in different indications warrant dose adjustments across different populations (i.e., due to disease burden).

Challenges

1. Phase II studies may appear to be the earliest opportunity to diversify trials. However, such studies typically have a relatively small sample size. There is a high uncertainty of PK, safety, and PD datasets. Furthermore, increased costs associated with opening additional sites may limit the concept of phase I/phase Ib studies to be diversified a priori.
2. Oftentimes, dedicated CP studies are performed with very specific objectives to study the particular end points related to DDI, formulation or effect of food, etc. Allowing diverse populations in dedicated CP studies may introduce variability and confound the interpretation of results thereby impacting the primary study objectives.
3. For investigational trials, first-inpatient studies (not enrolling healthy participants) are often performed in late-line patients where all prior therapies have failed to provide benefit; sometimes, surrogate populations may also be enrolled for cost efficiency and ease of recruitment. As target populations of pivotal studies may sometimes be different from the phase-1b/2a populations, diversity planning conducted during early stages may require substantial amendments after recommended phase II dose (RP2D)/phase III dose has been selected (e.g., concomitant medications for patients seeking an earlier line of therapy may be different than for patients in late-line care).
4. Combination drug development brings additional challenges for fulfilling diversity goals. Response of individual monotherapies vs. combination products (and any overlapping toxicities or synergies for efficacy) in demographically diverse populations may also need additional considerations on a case-by-case-basis, when addressing DPs using quantitative pharmacology concepts.

Conclusions

The 2022 FDA Guidance provides a framework for sponsors to plan for the inclusion of broader populations in pivotal CT through DPs. Submission of a DP will facilitate a dialogue between the sponsors and agency to discuss the measures that sponsors could take to support exposure-safety/efficacy across broader demographics of age, sex/gender, race/ethnicity, and comorbidities within the indication. While the current draft guidance is focused on the applicability of DPs during drug development and marketing applications within the US healthcare system, the recommendations made in this white paper should be applicable to global drug development and to supporting diversity in regions. Additionally, while the draft guidance is focused on race/ethnicity, the ultimate goal is to assess the safety, efficacy, and PK of investigational drugs in demographically representative patient populations for whom the new therapy is eventually intended. The D&I WG within IQ CPLG concludes that within the pharmaceutical industry, there is awareness of the FDA draft guidance and of the expectation of submission of DPs at the latest by EoP2. Clinical pharmacologists are involved in contributing to these plans and are using cumulative understanding from interventional and observational studies as well as applying MIDD principles to drafting these plans. Growing knowledge of biology, physiology, genetics, disease characteristics, and the influence of extrinsic factors coupled with greater computing ability has expanded the possibilities for predictive tools to make a strong case for widening inclusion/exclusion criteria for global trials. With a wealth of data at our fingertips, partnerships with regulators and patient advocates, and with clinical pharmacologists at the cross-section of multidisciplinary functionalities to consider safety, efficacy, covariates' effects, disease characteristics, and disease prevalence, this discipline is well-positioned to support trial diversification.

Figure 8 Word Cloud summarizing the multiple dimensions of D&I in global clinical trials.

This effort should be conducted in partnership with disciplines including safety, biostatistics, clinical, regulatory, drug metabolism/disposition, and patient advocacy. The near-term success of the D&I initiative might involve ensuring that every clinical program has a DP and has a framework that will evolve based on discussion between industry and health authorities.

It is acknowledged that including an indication-relevant diverse and inclusive population can be challenging, emphasizing the role of model-based analyses and extrapolation of learnings from global datasets, whenever the opportunity exists. In addition, it is vital to have an early understanding of the PK and PD in the population of interest or a suitable surrogate population during early clinical studies through observed data and use of virtual patient populations. Through a model-based approach, clinical pharmacologists can lower the barrier of entry for underrepresented populations into late-phase studies and ascertain if the inclusion/exclusion criteria are well informed by available data to ensure that the right patient is given the right dose (**Figure 8**).

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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1. FDA. US FDA Drug Trial Snapshot (2020).
2. Campbell, A.D. *et al*. An analysis of racial and ethnic backgrounds within the CASiRe international cohort of sickle cell disease patients: implications for disease phenotype and clinical research. *J. Racial Ethn. Health Disparities* **8**, 99–106 (2021).
3. Masese, R.V. *et al*. Effective recruitment strategies for a sickle cell patient registry across sites from the sickle cell disease implementation consortium (SCDIC). *J. Immigr. Minor. Health* **23**, 725–732 (2021).
4. Anaba, U. *et al*. Diversity in modern heart failure trials: where are we, and where are we going. *Int. J. Cardiol.* **348**, 95–101 (2022).
5. Abrahamowicz, A.A., Ebinger, J., Whelton, S.P., Commodore-Mensah, Y. & Yang, E. Racial and ethnic disparities in hypertension: barriers and opportunities to improve blood pressure control. *Curr. Cardiol. Rep.* **25**, 17–27 (2023).
6. Hwang, T.J. & Brawley, O.W. New federal incentives for diversity in clinical trials. *N. Engl. J. Med* **387**, 1347–1349 (2022).
7. FDARA. Section 610(a)(1) of FDARA, 131 Stat. 1005, Public Law 115–52 (August 18, 2017) (2016).
8. FDA U,Food and Drug Administration. Diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials: draft guidance for industry (2022).
9. FDA U. FDA offers guidance to enhance diversity in clinical trials, Encourage inclusivity in medical product development (2020).
10. Gross, A.S., Harry, A.C., Clifton, C.S. & Della, P.O. Clinical trial diversity: an opportunity for improved insight into the determinants of variability in drug response. *Br. J. Clin. Pharmacol.* **88**, 2700–2717 (2022).
11. Masters, J.C. *et al*. Ensuring diversity in clinical trials: the role of clinical pharmacology. *Contemp. Clin. Trials* **118**, 106807 (2022).
12. Lackland, D.T., Sims-Robinson, C., Jones Buie, J.N. & Voeks, J.H. Impact of COVID-19 on clinical research and inclusion of diverse populations. *Ethn. Dis* **30**, 429–432 (2020).

13. Corbie-Smith, G. The continuing legacy of the Tuskegee syphilis study: considerations for clinical investigation. *Am. J. Med. Sci.* **317**, 5–8 (1999).
14. Shahzad, M. *et al*. Geographic and racial disparities in chimeric antigen receptor-T cells and bispecific antibodies trials access for diffuse large B-cell lymphoma. *Clin. Lymphoma Myeloma Leuk.* **24**, 316–322 (2024).
15. Fowler, H. *et al*. Comorbidity prevalence among cancer patients: a population-based cohort study of four cancers. *BMC Cancer* **20**, 2 (2020).
16. Ng, H.S., Vitry, A., Koczwara, B., Roder, D. & McBride, M.L. Patterns of comorbidities in women with breast cancer: a Canadian population-based study. *Cancer Causes Control* **30**, 931–941 (2019).
17. MacRae, C., Mercer, S.W., Guthrie, B. & Henderson, D. Comorbidity in chronic kidney disease: a large cross-sectional study of prevalence in Scottish primary care. *Br. J. Gen. Pract.* **71**, e243–e249 (2021).
18. Zhao, P. *et al*. Evaluation of exposure change of nonrenally eliminated drugs in patients with chronic kidney disease using physiologically based pharmacokinetic modeling and simulation. *J. Clin. Pharmacol.* **52**(1 Suppl), 91s–108s (2012).
19. Younis, I.R., Wang, F. & Othman, A.A. Feasibility of using population pharmacokinetics-based virtual control groups in organ impairment studies. *J. Clin. Pharmacol.* **64**, 713–718 (2024).
20. Suri, A., Chapel, S., Lu, C. & Venkatakrishnan, K. Physiologically based and population PK modeling in optimizing drug development: a predict-learn-confirm analysis. *Clin. Pharmacol. Ther.* **98**, 336–344 (2015).
21. Heimbach, T. *et al*. Physiologically-based pharmacokinetic modeling in renal and hepatic impairment populations: a pharmaceutical industry perspective. *Clin. Pharmacol. Ther.* **110**, 297–310 (2021).
22. Shen, J., Moore, K.T., Shukla, S., Yeo, K.R. & Venkatakrishnan, K. Inclusion of obese participants in drug development: reflections on the current landscape and a call for action. *J. Clin. Pharmacol.* **64**, 13–18 (2024).
23. Yoshihara, K., Fukae, M., Kastrissios, H., Wada, R. & Shimizu, T. Exposure-response analysis of the efficacy and safety of esaxerenone, a novel nonsteroidal mineralocorticoid receptor blocker, in hypertensive patients with or without diabetic kidney disease. *Drug Metab. Pharmacokinet.* **55**, 100535 (2023).
24. Deiteren, A., Coenen, E., Lenders, S., Verwilst, P., Mannaert, E. & Rasschaert, F. Data driven evaluation of healthy volunteer characteristics at screening for phase I clinical trials to inform on study design and optimize screening processes. *Clin. Transl. Sci.* **14**, 2450–2460 (2021).
25. Garnett, C. *et al*. Scientific white paper on concentration-QTc modeling. *J. Pharmacokinet. Pharmacodyn.* **45**, 383–397 (2018).
26. Goteti, K. *et al*. Opportunities and challenges of disease progression modeling in drug development – an IQ. *Perspectives* **114**, 266–274 (2023).
27. Kalliokoski, A., Neuvonen, P.J. & Niemi, M. SLCO1B1 polymorphism and oral antidiabetic drugs. *Basic Clin. Pharmacol. Toxicol.* **107**, 775–781 (2010).
28. Jiang, X.L., Samant, S., Lesko, L.J. & Schmidt, S. Clinical pharmacokinetics and pharmacodynamics of clopidogrel. *Clin. Pharmacokinet.* **54**, 147–166 (2015).
29. Liu, J., Cui, J.Y., Lu, Y.-F., Corton, J.C. & Klaassen, C.D. Sex-, age-, and race/ethnicity-dependent variations in drug-processing and NRF2-regulated genes in human livers. *Drug Metab. Dispos.* **49**, 111–119 (2021).
30. Ingelman-Sundberg, M. & Rodriguez-Antona, C. Pharmacogenetics of drug-metabolizing enzymes: implications for a safer and more effective drug therapy. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* **360**, 1563–1570 (2005).
31. Anderson, K.E. Influences of diet and nutrition on clinical pharmacokinetics. *Clin. Pharmacokinet.* **14**, 325–346 (1988).
32. Heymsfield, S.B., Peterson, C.M., Thomas, D.M., Heo, M. & Schuna, J.M. Jr. Why are there race/ethnic differences in adult body mass index-adiposity relationships? A quantitative critical review. *Obes. Rev.* **17**, 262–275 (2016).
33. Olafuyi, O., Parekh, N., Wright, J. & Koenig, J. Inter-ethnic differences in pharmacokinetics-is there more that unites than divides? *Pharmacol. Res. Perspect.* **9**, e00890 (2021).
34. Limdi, N.A. & Veenstra, D.L. Warfarin pharmacogenetics. *Pharmacotherapy* **28**, 1084–1097 (2008).
35. Profaizer, T. & Eckels, D. HLA alleles and drug hypersensitivity reactions. *Int. J. Immunogenet.* **39**, 99–105 (2012).
36. Sabatine, M.S. PCSK9 inhibitors: clinical evidence and implementation. *Nat. Rev. Cardiol.* **16**, 155–165 (2019).
37. Klopp-Schulze, L. *et al*. Asia-inclusive global development of Enpatoran: results of an Ethno-bridging study, intrinsic/extrinsic factor assessments and disease trajectory modeling to inform Design of a Phase II multiregional clinical trial. *Clin. Pharmacol. Ther* **115**, 1346–1357 (2024).
38. Kelleher, D.L. *et al*. Safety, tolerability, pharmacodynamics and pharmacokinetics of umeclidinium and vilanterol alone and in combination: a randomized crossover trial. *PLoS One* **7**, e50716 (2012).
39. PMDA. Basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan (2023).
40. Caudle, K.E. *et al*. Incorporation of pharmacogenomics into routine clinical practice: the clinical pharmacogenetics implementation consortium (CPIC) guideline development process. *Curr. Drug Metab.* **15**, 209–217 (2014).
41. Picard, N., Rouguieg-Malki, K., Kamar, N., Rostaing, L. & Marquet, P. CYP3A5 genotype does not influence everolimus in vitro metabolism and clinical pharmacokinetics in renal transplant recipients. *Transplantation* **91**, 652–656 (2011).
42. Sawant Basak, A. *et al*. Metabolism and clinical pharmacokinetics of 2-methyl-n-(2′-(pyrrolidinyl-1-ylsulfonyl)-n-[1,1′-biphenyl]-4-yl) propran-1-amine: insights into monoamine oxidase- and CYP-mediated disposition by integration of in vitro ADME tools. *Xenobiotica* **44**, 438–454 (2014).
43. Cahn, A., Mehta, R., Preece, A., Blowers, J. & Donald, A. Safety, tolerability and pharmacokinetics and pharmacodynamics of inhaled once-daily umeclidinium in healthy adults deficient in CYP2D6 activity: a double-blind, randomized clinical trial. *Clin. Drug Investig.* **33**, 653–664 (2013).
44. Cerny, M.A., Spracklin, D.K. & Obach, R.S. Human absorption, distribution, metabolism, and excretion studies: origins, innovations, and importance. *Drug Metab. Dispos.* **51**, 647–656 (2023).
45. Feng, S. *et al*. Combining Bottom-Up and Top-Down methods to assess ethnic difference in clearance: Bitopertin as an example. *Clin. Pharmacokinet.* **55**, 823–832 (2016).
46. Liao, M.Z. *et al*. Ethnic sensitivity assessment: Polatuzumab vedotin pharmacokinetics in Asian and non-Asian patients with previously untreated diffuse large B-cell lymphoma in POLARIX. *Clin. Transl. Sci.* **16**, 2744–2755 (2023).
47. Fediuk, D.J. *et al*. End-to-end application of model-informed drug development for ertugliflozin, a novel sodium-glucose cotransporter 2 inhibitor. *CPT Pharmacometrics Syst. Pharmacol.* **10**, 529–542 (2021).
48. Jamei, M. Recent advances in development and application of physiologically-based pharmacokinetic (PBPK) models: a transition from academic curiosity to regulatory acceptance. *Curr. Pharmacol. Rep.* **2**, 161–169 (2016).
49. Shebley, M. *et al*. Physiologically based pharmacokinetic model qualification and reporting procedures for regulatory submissions: a consortium perspective. *Clin. Pharmacol. Ther.* **104**, 88–110 (2018).
50. Lin, J. *et al*. Investigation of CYP3A induction by PF-05251749 in early clinical development: comparison of linear slope physiologically based pharmacokinetic prediction and biomarker response. *Clin. Transl. Sci.* **15**, 2184–2194 (2022).
51. Ramamoorthy, A., Pacanowski, M.A., Bull, J. & Zhang, L. Racial/ethnic differences in drug disposition and response: review of

recently approved drugs. *Clin. Pharmacol. Ther.* **97**, 263–273 (2015).
52. Mulinari, S., Vilhelmsson, A., Ozieranski, P. & Bredström, A. Is there evidence for the racialization of pharmaceutical regulation? Systematic comparison of new drugs approved over five years in the USA and the EU. *Soc. Sci. Med.* **280**, 114049 (2021).
53. Deere, B.P. & Ferdinand, K.C. Hypertension and race/ethnicity. *Curr. Opin. Cardiol.* **35**, 342–350 (2020).
54. FDA U. Best Pharmaceuticals for Children act and Pediatric Research Equity act (2015).
55. FDA U. Pediatric Drug Development: Regulatory Considerations — Complying with the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity under the Best Pharmaceuticals for Children act (2023).
56. EMA. Guidance for Stepwise PIP pilot (2020).
57. Barrett, J.S. *et al*. Challenges and opportunities in the development of medical therapies for pediatric populations and the role of extrapolation. *Clin. Pharmacol. Ther.* **103**, 419–433 (2018).
58. Severin, T. *et al*. How is the pharmaceutical industry structured to optimize pediatric drug development? Existing pediatric structure models and proposed recommendations for structural enhancement. *Ther. Innov. Regul. Sci.* **54**, 1076–1084 (2020).
59. FDA U. Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials Guidance for Industry. 2019.
60. Fernandez, E., Perez, R., Hernandez, A., Tejada, P., Arteta, M. & Ramos, J.T. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmaceutics* **3**, 53–72 (2011).
61. Atia, O. *et al*. Outcomes, dosing, and predictors of vedolizumab treatment in children with inflammatory bowel disease (VEDOKIDS): a prospective, multicentre cohort study. *Lancet Gastroenterol. Hepatol.* **8**, 31–42 (2023).
62. Momper, J.D. *et al*. Adolescent dosing and labeling since the Food and Drug Administration amendments act of 2007. *JAMA Pediatr.* **167**, 926–932 (2013).
63. CDC (2015).
64. Mehta, R., Kelleher, D., Preece, A., Hughes, S. & Crater, G. Effect of verapamil on systemic exposure and safety of umeclidinium and vilanterol: a randomized and open-label study. *Int. J. Chron. Obstruct. Pulmon. Dis.* **8**, 159–167 (2013).
65. Bi, Y. *et al*. Model-informed drug development approach supporting approval of adalimumab (HUMIRA) in adolescent patients with hidradenitis suppurativa: a regulatory perspective. *AAPS J.* **21**, 91 (2019).
66. FDA U. Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs: Notice (1993).
67. Meibohm, B., Beierle, I. & Derendorf, H. How important are gender differences in pharmacokinetics? *Clin. Pharmacokinet.* **41**, 329–342 (2002).
68. Cirrincione, L.R. & Huang, K.J. Sex and gender differences in clinical pharmacology: implications for transgender medicine. *Clin. Pharmacol. Ther.* **110**, 897–908 (2021).
69. Valentine, S.E. & Shipherd, J.C. A systematic review of social stress and mental health among transgender and gender non-conforming people in the United States. *Clin. Psychol. Rev.* **66**, 24–38 (2018).
70. Rich, A.J., Scheim, A.I., Koehoorn, M. & Poteat, T. Non-HIV chronic disease burden among transgender populations globally: a systematic review and narrative synthesis. *Prev. Med. Rep.* **20**, 101259 (2020).
71. Streed, C.G. Jr. *et al*. Assessing and addressing cardiovascular health in people who are transgender and gender diverse: a scientific statement from the American Heart Association. *Circulation* **144**, e136–e148 (2021).
72. Lehr, T. *et al*. Dabigatran etexilate in atrial fibrillation patients with severe renal impairment: dose identification using pharmacokinetic modeling and simulation. *J. Clin. Pharmacol.* **52**, 1373–1378 (2012).
73. Maass, K.F. *et al*. Leveraging patient-centric sampling for clinical drug development and decentralized clinical trials: promise to reality. *Clin. Transl. Sci.* **15**, 2785–2795 (2022).