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Diversity, Equity and Inclusion in Clinical Research

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Executive Summary

Fair and timely access to medicines underpins one of several important tenets within the Life Science industry and the emerging Environmental, Social and Corporate (ESG) framework. As covered in this paper, it is important that the Life Sciences sector, regulators and other relevant stakeholders promote evidence-based enrolment of diverse patient groups into clinical trials. As we outline below, by building an infrastructure and framework which promote the inclusion of diverse patients, who represent the intended patient population, can lead to improved patient safety and efficacy for new medicines.

Clinical Research in Diverse Populations Matters

Traditional Randomized Clinical Trials (RCTs) continue to form the backbone of clinical and safety evidence submitted to health authorities for regulatory review, a risk-benefit approach underpins the decision-making process to approve clinical trials, human drugs, drug/device combinations and advanced therapy medicinal products for licensing. It is well-established that safety and efficacy data is highly influenced by internal (intrinsic: ethnicity, sex, age and genetic background) and external (extrinsic: climate, education, accessibility to healthcare) factors. The challenge for regulators and life science companies is that safety and efficacy data from a randomized clinical trial may not always translate to the real world 'effectiveness' of a medicine (how efficacious the drug is in patients once marketed) which is governed by complex intrinsic and extrinsic factors, addressed in ICH E5 R1 guidance – see figure 1.

To mitigate against a potentially lower drug efficacy or a different drug safety profile in a wider population vs the efficacy and safety findings evidenced in RCTs; it is important for Sponsors to include patient orientated outcomes (relief of symptoms) alongside traditional endpoints (blood pressure, glucose concentrations). The diversity of clinical trial participants in the context of disease prevalence is key to capturing patient orientated outcomes in representative populations. In this article we discuss how intrinsic and extrinsic factors – emphasising 'diversity in clinical trials' - should be placed at the forefront of sponsors minds when designing clinical trial protocols and long-term follow up activities.

Figure 1 - Classification of intrinsic and extrinsic ethnic factors (image taken from ICH E5 (R1)[1]

Intrinsic		Extrinsic
Genetic	Physiological and pathological conditions	Environmental
Gender	Age (children - elderly)	Climate Sunlight Pollution
Height Bodyweight	Liver Kidney Cardiovascular functions	**Culture** Socio-economic factors Educational Status Language
ADME Receptor Sensitivity		Medical practice Disease definition/Diagnostic Therapeutic approach Drug compliance
Race		Smoking Alcohol
Genetic polymorphism of the drug metabolism		Food habits Stress
Genetic disease	Diseases	Regulatory practice/GCP Methodology/Endpoints

Nuances of Sex and Gender in Clinical Trials

Adverse drug reactions (ADRs) are responsible for approximately 5% of unplanned hospital admissions: a major health concern[2]. Research has demonstrated that women are 1.5-1.7 times more likely to develop ADRs[3]. It has also been shown that women report twice as many ADRs compared to men[4]. In a separate study, which utilised global post-marketing surveillance data, it was shown that of 15 million ADR reports collected between 1967 and 2018, 60.1% of reports were from females and 39.9% from males[5].

A systemic review of over 5000 articles demonstrated that 86 FDA approved medicines [including antidepressants, cardiovascular, anti-seizure and pain-medication were shown to have markedly different ADR profiles between the sexes[6]. Of 86 drugs studied the majority showed elevated blood concentration and longer elimination time in women, with the ADRs being shown to be strongly linked to PK differences seen in women at the clinical trial stage. For 59 of the drugs reviewed, sex-related pharmacokinetic profiles were predictive of 88% of ADRs. In females, sex-related PK data was predictive of ADRs for 96% of drugs reviewed versus 29% in males. These findings suggested that elevated drug concentrations and decreased drug elimination times are far more prevalent in women than men, which may significantly impact safety.

There is emerging evidence that both sex and gender can influence how an individual selects a medicine and responds to treatment, and how they metabolize and adhere to drug regimens[7]. Two common questions asked by clinical researchers are (1) Should the sex or gender of study participants be reported? and (2) What is the correct term for designating males and females or men and women? At present there are no validated tools available to clinical researchers for assessing gender, even though failing to account for gender may lead to inaccurate results, therefore we would expect advances to be made in this area in the future.

Other important factors such as sexual orientation have led to well documented health disparities in LGBTQI+ communities[8]. A 2010 study showed that 37 of 243 clinical trials conducted in relation to couples and sexual function after applicable medical treatments excluded people in same-sex relationships[9]. Whilst there is a requirement for sound scientific reasoning for the exclusion of trial participants, on the basis of sex and/or ethnicity, the same level of oversight may not be applicable to members of the LGBTQIA+ community, leading to disproportionate representation and / or misrepresentation in clinical trials.

Ethnicity - Overcoming Critical Barriers

Randomized Clinical Trial data is the corner stone of drug development, however, proposed patient groups are rarely homogenous in nature and patient groups are increasingly demanding that life science companies accurately reflect this heterogeneity in trial data, increasing the accuracy of outcomes and the predictive nature of the risk-benefit profile of a licensed treatment, especially in formerly under-represented demographic groups. In two separate reviews of new molecular entities (NME) approved by the Food and Drug Administration (FDA) between 2008-2013 and 2014-2019, it was shown there is a marked difference in exposure and response across racial and ethnic groups[10] [11]. Specifically, difference in pharmacodynamic response and/or pharmacogenetics, pharmacokinetic and safety profiles were noted in 20% of the 167 NMEs in the 2008-2013 review, and 10% of the 261 NME's included in the 2014-2019 review.

An example of this is the increased risk of a hypersensitivity reaction to the antiseizure drug carbamazepine in patients of South -East Asian[12] origin .The HLA-B*15:02 allele is strongly associated with carbamazepine-induced Stevens Johnson/ toxic epidermal necrolysis in Southeast Asian populations where this allele is most common.

Population Pharmacokinetics – an Opportunity to Improve Insight

It is important that the life science industry understand population pharmacokinetics (popPK) within subjects as early as possible in the drug development pathway, and this includes the utilisation of tools available to ensure they capture data from a diverse pool of individuals It was recently reported that 96% of patients included in genetic studies for Alzheimer's Disease and Type 2 diabetes between 2000 and 2009 were of European ancestry. By 2016, 81% were of European descent, but only 0.08% were of Arab or Middle Eastern descent[13]. Yet in the same year it was reported that in the Middle Eastern region the number of people with diabetes is projected to increase by 96.2% by 2035[14]. Moreover, in 2019, the highest prevalence of diabetes in the world at 12.2%, with its associated morbidity and mortality, was found in the Middle East and North Africa region[15] Sponsors should consider early engagement with patient advocacy groups and patients to gather suggestions for designing trials in which participants from underrepresented patient groups would be willing to participate and support research activities.

The life science industry should consider the consequences of not having an appropriately diverse clinical trial dataset. Several companies have had to invest additional resource and time after pivotal studies were completed to address potential population-specific prescribing recommendations, post-marketing studies and regional differences in drug approval, following the identification of gaps in clinical trial data, as a consequence of poor patient representation. In a review of drugs approved by the FDA. Between 2008 and 2013, of the 167 new molecular entities (NME) documented, racial/ethnic subgroup analysis showed a reported difference in pharmacokinetics, safety and efficacy in nineteen, five and three NMEs, respectively[16] . Of this group, four NMEs required race/ethnicity based post-marketing studies, one was a post-marketing requirement whilst the other three were post-marketing commitments (see Table 1). More recently, between 2014 and 2019, of the 261 approved NMEs, six required post-marketing studies based on racial/ethnic differences[17] . In February 2022, the drug Sintilimab was rejected by the FDA because the data generated from clinical trials was not representative of the U.S population[18]. Clinical trial data was derived solely from China; hence the pharmacokinetic data generated was considered insufficient to make a definitive conclusion regarding applicability to a racially diverse U.S patient population

Table 1- Race/ethnicity-related post marketing requirement/commitment for the new molecular entities approved by the FDA (2008-2013). Table adapted from Ramamoorthy et al., 2015

Drug (approval date)	Post-Marketing Measures
Belimumab (2011)	Conduct a randomized, controlled clinical trial to evaluate the efficacy and safety in African American patients with systemic lupus erythematosus.
Ioflupane I-123 (2011)	Conduct a clinical trial that assesses the agreement between imaging results and diagnostic outcomes among non-Caucasian and Caucasian patients.
Telaprevir (2011)	Conduct a trial to evaluate treatment response and safety among blacks/African Americans compared to non-blacks/African Americans
Simeprevir (2013)	Clinical trial to assess signals of serious risk of increased frequency of adverse events (including rash, photosensitivity, pruritus, dyspnea and increased bilirubin) in patients of East Asian ancestry.

Older Adults – Promoting Inclusion in Clinical Research

Population PK conclusions have been historically supported by modelling and simulation of new treatments in populations inherently difficult to study (pregnant women, geriatric patients). With the current emphasis on inclusivity in clinical trials being supported by a series of new guidance documents globally; trials of drugs to treat cancers that disproportionately affect older adults i.e., pancreatic cancer is imperative. New FDA guidance is now available to support the inclusion of adults aged ≥65 in cancer clinical trials[19].

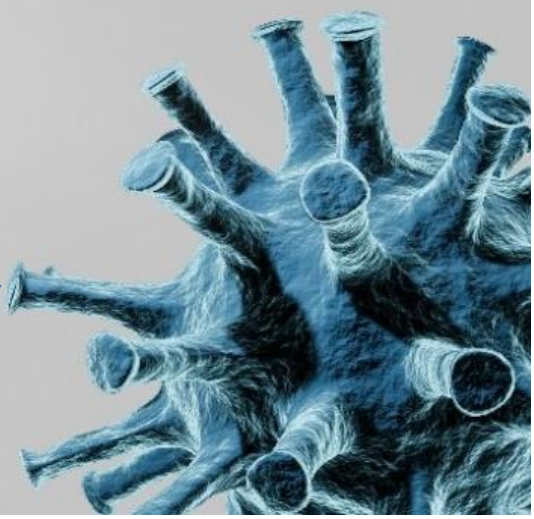
The objective, as discussed above (with respect to sex, gender and ethnicity), is to bridge between efficacy and effectiveness in sub-populations. Older adults are not formerly excluded from cancer trials, however evidence suggests that they remain under-represented. It is important that Sponsors consider broader patient participation in studies which would help generate datasets used to improve the evidence base for treating this patient population. By doing so it would better inform healthcare professionals with specific labelling, as well as describing use in older adults with impaired renal, cardiac, and hepatic function, concomitant medication requirements, and comorbidity considerations - all of which affect drug disposition and response in this sub-population[20]

COVID-19 and Vaccine Development

Following the global COVID-19 pandemic, vaccine development became a global pharmaceutical priority. Vaccines approved for public use require comprehensive RCTs to establish their safety and efficacy. The demographics of vaccine trial participants should reflect the vulnerable groups to whom infection presents the greatest risk of harm and mortality.

Research has shown a disproportionate rate of COVID-19 infection and mortality among the elderly, minority ethnic groups and socially deprived groups with longstanding social deprivation. In the UK, during the first wave of the COVID-19 pandemic, ethnic minority groups (with the exception of women in "Chinese" or "White Other" categories) had higher rates of death post-exposure compared with the "White British" population[21]

Deprivation is all encompassing and coincidentally in 2019 the UK Ministry of Housing, Communities and Local Government updated its English Indices of Deprivation 2019 (IoD2019) outlining the conflating indicators of depravation, which cover seven distinct domains of depravation that are appropriately weighted as follows: Income (22.5%), Employment (22.5%), Health Deprivation and Disability 13.5%), Education, Skills Training (13.5%), Crime (9.3%), Barriers to Housing and Services (9.3%), and Living Environment (9.3%) – further it has been shown that Asian and Black people are disproportionately represented within these domains. This data above is supported by the UK Office for National Statistics (ONS): 1st March and 17th April 2020 the deprived areas in England had more than double the mortality rate from COVID-19 than the least deprived areas[21].



These issues are not confined to the UK; in the US, some minority groups including Black, Latino, Pacific Islander and Indigenous peoples have been shown to have twice the COVID mortality rate of Caucasian people[22 23] .

Despite policies, guidelines, and regulations to promote the diversification of clinical trial groups by the European Medicines Agency and FDA, the inclusion of key demographic populations within clinical research continues to be less than proportionate to their representation in society. In a cross-sectional study of 230 US-based vaccine clinical trials it was shown members of racial/ethnic minority groups and older adults were underrepresented, whereas female adults were overrepresented[24] . This research indicates that enrolment should include targets for diversity, so that subsequent epidemiology data collection is appropriate and will lead to a meaningful data set for the medicinal product in question.

Redressing this imbalance in trial participation is not a simple task as the issue is compounded by ethnic disparities in vaccine hesitancy, underpinned by historical mistrust in healthcare organisations, government, and research, which is still prevalent in those affected communities. Factors influencing trust vary between ethnic groups. Reported experiences of discrimination, perceived structural inequalities, and concerns of trial under-representation[25] are likely to influence trust; of which the latter is within the remit of life science companies to acknowledge and address with appropriate measures to effect change. In the absence of diverse participation, individuals may not trust that data or that conclusions apply to them, and they may be highly sceptical of the resulting evidence base[26]

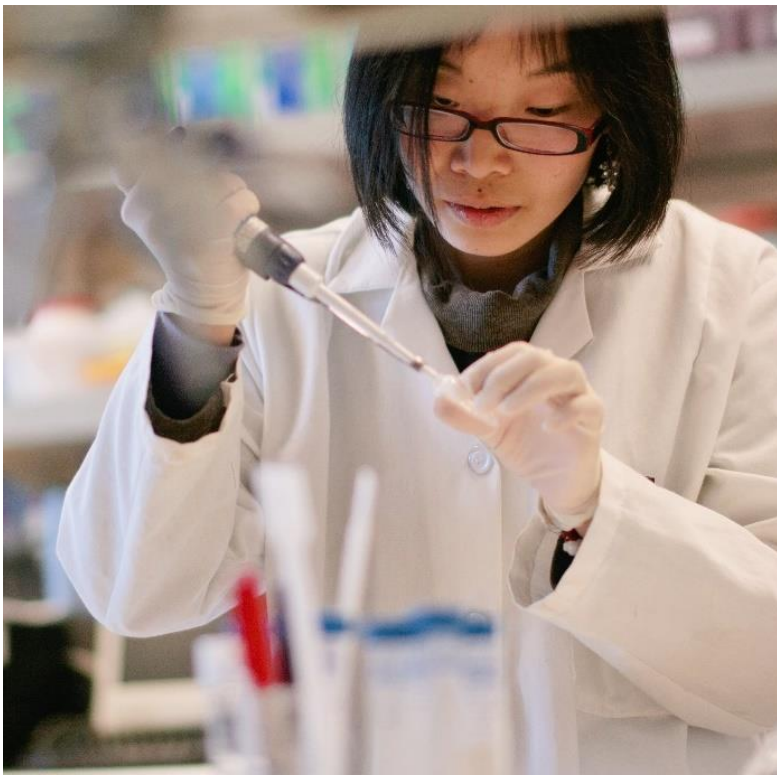
Inclusivity: Trial Participation

Regulations and Guidance

Diversity and inclusion in clinical research are now a high priority for all life science companies, as the industry strives to develop drugs that are effective in the intended patient population. Steps are being taken to address historic disparities. A multi-stakeholder's approach is recommended to understand the problem, and to analyse potential approaches to mitigate underrepresentation.

In Europe **The EU Clinical Trial Regulation No 536/2014** (which came into force in 2022), places an increased emphasis on diversifying clinical trials via fairer representation of sexes and age-groups, as depicted in the following text: **"Unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups, for example gender and age groups, that are likely to use the medicinal product investigated in the clinical trial".** It also contains additional prescriptive rules on the inclusion of pregnant and breastfeeding women in clinical trials. This deliberate and purposeful inclusion in research aimed to provide added protection for this vulnerable group. One of the stated aims of the Clinical Trials Regulation (CTR) is to ensure that Europe is a favourable environment to conduct clinical research with high standards of safety for clinical trial participants and public transparency. As part of the CTR initiation, the European Medicines Agency (EMA) launched the **Clinical Trial Information System (CTIS)** which will revolutionise and streamline the process for Clinical Trial applications (CTA) in the EU.

The CTIS is a globally unique system which is designed and anticipated to be a 'one stop shop' fulfilling the various steps in the CTA process from a regulatory and legal standpoint. There will be a phased approach to use of the CTIS with 31 January 2024 being the date by which all existing clinical trials need to be present in CTIS. It is hoped that the increased levels of transparency with CTIS for the public will lead to more awareness and knowledge of clinical research and may lead to more diversity in patient participation in future clinical trials, it will be interesting to monitor the evolution of CTIS and the EU transparency goals for CTR over the next few years.



To build on the application of the CTR and launch of the CTIS, the EMA, European Commission (EC) and the Heads of Medicines Agencies (HMA) have launched an initiative called **Accelerating Clinical Trials** in the EU, known as ACT EU [27]. The aim of this initiative is to improve and transform the way in which trials are initiated, designed and run to provide a more holistic approach that addresses patients' needs whilst maintaining the high-level of protection of data integrity, including trial participants and demonstrating the level of transparency that the public expects. Some of the strategic priorities of ACT EU for 2022/2023 include developing and publishing key methodologies guidance e.g., complex trials, decentralized trials; In vitro diagnostic medical device (IVDR)/CTR, supporting modernization of good clinical practice (GCP) informed by International Conference on Harmonization (ICH) guidance and delivering a comprehensive clinical trials training curriculum. Additionally, in recognition of the fact that there is work to be done on Europe as a research environment, a key performance indicator (KPI) will be established to track performance and measure engagement of research centres in member states with the aim of increasing diversity across clinical research and strengthening and energizing the **European Research Network (ERN).**

Whilst progressive, the onus will be on the Sponsor to meet these additional requirements. It is unclear whether a study would be accepted or not if trial participants were not an accurate reflection of the intended patient population. What is clear, is that previous EU guidance was not prescriptive enough, as data gaps remained regarding the homogeneity of trial participants.

In the US, new FDA guidance: "Enhancing the Diversity of Clinical Trial Populations--Eligibility Criteria, Enrolment Practices, and Trial Designs" was published in 2020. This guidance aims to encourage the broadening of eligibility criteria in clinical trials through inclusive trial practices, trial designs, and methodological approaches. This includes recommendations for sponsors to improve the quality of trials via the active enrolment of underrepresented populations into clinical trials. The FDA guidance is wider in scope and includes suggestions and signposting to promote the enrolment of diverse trial participants, including women of childbearing potential, pregnant women, racial and ethnic minorities, children, and older adults. Assisting sponsors with the tools to enable diverse patient recruitment, has a pivotal role in improving access to medicines. Further consultation between the life science industry and regulators will be required to ensure that new and proposed guidance are as impactful as anticipated.

In the UK, as of 1 January 2022, combined review is the way all new Clinical Trials of Investigational Medicinal Products (CTIMPS) applications (including IMP/Device combinations) must be made. Submissions will be via the Integrated Research Application System (IRAS).

The advantage to sponsors of coordinated review, a single submission for Clinical Trial Authorisation (CTA) and Research Ethics Committee (REC) opinion; and subsequent combined, real-time communications for requests for further information available to view on the IRAS dashboard. This streamlined application and review process will allow end-to-end lifecycle management via IRAS, including any urgent safety reporting and subsequent substantial amendments to trial authorisations, end of trial notifications and submission of summary results.

It is hoped that this new combined review service will allow for '30% reduction in time to trial set up' assisting the timely delivery of clinical research across all phases. This aligns with future proposals to streamline the clinical trial application process. The MHRA recently published an open consultation (17 January 2022) entitled 'Proposal for Legislative Change for Clinical Trials' - one of the key points to be addressed will be drawing on the expertise and experiences of trial participants, working in partnership with communities in the design, management, conduct of a trial; creating opportunities to address health inequalities, improve enrolment and retention of participants

Future Considerations

Practical steps

To improve trust from minority patient groups, industry stakeholders must improve communication and engagement. This starts with taking necessary steps to improve patient awareness of clinical trials and allow for better ease of access, both practically, in terms of selection of site locations and accessibility, and comprehensibility, e.g., use of patient friendly marketing material that target a wider range of demographics (multi-lingual; use of digital platforms). Engagement with patient groups and organisations should take place during clinical trial planning, and as early as possible in the drug development pathway. Early engagement will facilitate a trial design that is fit-for-purpose, including patient perspectives on improving enrolment and continued patient engagement with trials. For example, financial burdens (e.g., distance, number of visits) on individuals taking part in trials may prevent enrolment and participation. Consideration should also be given to meeting patients in situ, or the use of community-based clinical trial infrastructure utilising pharmacies and other community healthcare centres as part of a trial to serve underrepresented populations. This could have the joint effect of improving access while lessening the burden of travel and distance to sites, as well as having health care providers in communities building trust in the clinical trial process

Can digital technology and advances in clinical trial processes improve patient accessibility and enrolment?

With the inevitable advancement of digital technologies and the implementation in clinical research it would be pertinent to explore the role these technologies may have in harvesting data from a clinical trial participant. Digital technologies can cover a broad range of applications, and include but are not limited to mobile health (mHealth) tools (e.g. wearable device carried by patients to measure certain health related parameters, remote patient monitoring) and tele-healthcare in clinical trials (e.g. video consultations), health data analytics (e.g. data processing systems that support bioinformatics modelling) and digital record systems (e.g. digital applications, also referred to as "apps", that function as patient diaries)[28]. Once stakeholders are confident that technologies are adequately validated, selection, based on scientific and ethical considerations can be presented to regulators in accordance with applicable legal and regulatory frameworks. The possibilities are endless, and in the context of trial participation and access to medicine technologies could assist:

- Reduced assessment times and hence increased patient compliance
- Improving access to individuals with rare diseases in remote settings
- Reasonable adjustments for to allow equal access for individuals with disabilities
- Patient engagement from marginalised groups with a preference for remote access

To address the implementation of computerised systems, (including instruments, software and services) used in clinical trials in the creation/capture of electronic clinical data the EU EMA have recently published the 'Guideline on computerised systems and electronic data in clinical trials'. It is acknowledged that digital technology is no utopia, the development of guidance to support companies conducting the risk-assessment of selected computer systems including ensuring integrity of derived clinical trial data is welcomed. It is important for all digital healthcare tools to comply with national and supranational data protection legislation governing the processing of patient health data, where legislation falls outside the scope of medicines regulations. However, if considered early in the drug development plan, compliance is by no means insurmountable and would be offset by the benefits of digital healthcare tools for patient engagement. The adoption of digital healthcare tools in clinical research accelerated dramatically during the COVID 19 pandemic and it is expected that such tools will continue to contribute to clinical research in the future

As discussed above fair and timely access to medicines underpins one of several important tenets within the Life Science industry and emerging ESG framework. Keeping abreast of innovative regulatory pathways and services being implemented by health authorities; payers and patient groups globally is critical for all companies. The KPMG Life Sciences Regulatory Solutions Practice is keen to support life science companies address health inequalities and meet their Environmental Social and Governance objectives as we move to an era of impactful change across all sectors.

The Regulatory Solutions team consists of technical experts with decades of experience in delivering strategic regulatory advice and regulatory risk management services for clients across critical markets, we have access to validated regulatory intelligence databases and are continually monitoring changing regulatory obligations and systems globally for our clients. As we look to the future, KPMG Life Science Regulatory Solutions Practice can assist pharmaceutical companies to address the challenges presented in this article

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