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How the FDA Sped Up Cancer Product Development and Reviews During a Global Pandemic

How to Streamline a Complex Process: The Value Add of Experienced Medical Writers for Oncology Dossiers

Asia's Clinical Trial Industry Developments and Challenges

Optimising Trials Assessing Cognitive Post-Acute Sequelae of SARS-CoV-2 (PASC-Cog)

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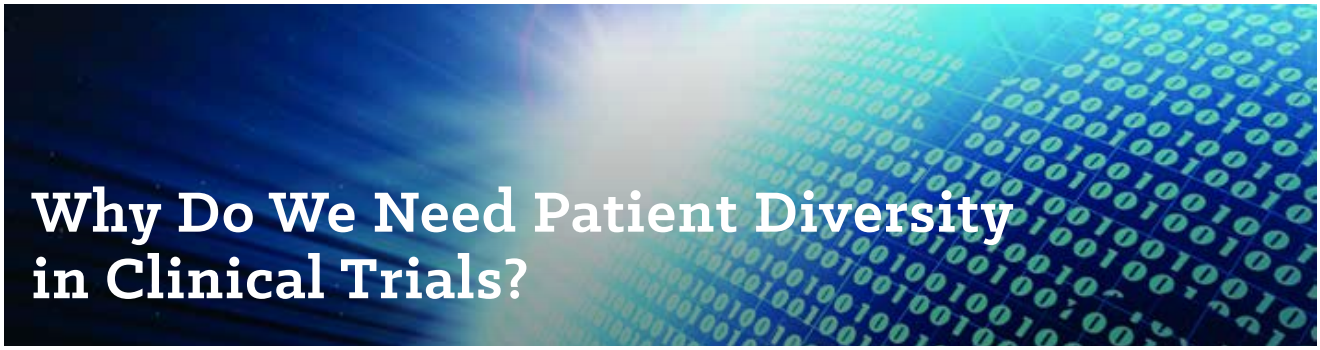

Why Do We Need Patient Diversity in Clinical Trials?

Ensuring Drug Safety, First and Foremost, Even Ahead of Drug Efficacy

In the commercialisation of new medications, the paramount legal responsibilities of the pharmaceutical company are, firstly, to prove that the pharmacology is safe and well understood, and, secondly, to prove effectiveness against the targeted disease. Within the European Union, for example, each pharmaceutical company has a Qualified Person for Pharmacovigilance (QPPV) representing them in each country in which they legally operate and market medications. The QPPV is legally responsible for the safety of a pharmaceutical product marketed for human usage in their country and do so by investigating adverse drug reactions (ADRs) – especially life-threating ones – reported by patients or their physicians in the country, associated with the use of their product(s). The identification of these emerging 'safety signals' guarantees the safety profiles of products marketed in that country.[1]

Pharmacovigilance consists of monitoring and ensuring drug safety across what are often diverse populations following a drug's market authorisation. As an example, in oxidative metabolism (a mechanism by which compounds are broken down in the body), there is extensive population variability in the key cytochrome P450 (CYP450) liver enzymes. A medication's metabolism and clearance (pharmacokinetics) are important factors when determining appropriate dosage for clinical efficacy. If an individual patient´s CYP450 enzyme activity is lower than anticipated, they will receive a comparatively higher dose, as, for them, the molecule will be metabolised and excreted at a relatively lower rate. Hence, repeated administration of the medication could lead to accumulation of the drug and increase the potential for toxicity.[2,3]

CYP450 enzymes are just one example of differential gene expression leading to varied pharmacodynamics and drug response. As drug treatments become increasingly personalised and often genetically focused, such as in cancer and many rare diseases, understanding genetic diversity across populations in countries in which the drug is marketed is increasingly critical. Taking it one step further, relatedness of populations and genetic ancestry across borders are also becoming important to trait mapping and the understanding of underlying genetic dependencies in populations of target countries, especially those with mixed populations.

As an illustration, there are significant differences in optimal dosing for East Asian populations, compared to populations of European, Latino or African descent when prescribing Warfarin. The medication is widely prescribed as an anticoagulant to prevent thromboses and embolisms, but there are population differences associated with genetic polymorphisms in the Warfarin metabolic pathway. As an example, there can be significant variations in the Vitamin K epoxide reductase complex gene which regulates Vitamin K as part of the inverse clotting synthetic pathway. Individuals of Asian descent require a lower dose of Warfarin compared to Latinos, who are still more sensitive to the medication than patients of European and African descent, which results in the need for specific per patient dosing and diet monitoring.[4,5,6]

Nature versus Nurture

Accounting for this genomic variability is therefore of importance for clinical trials, and the underlying reason for the need to ensure diversity in clinical trial patient populations. Additionally, the social and economic determinants of health must also be considered for the population of each country: there are significant differences in incidence of disease because of location, race, social status, and proximity to care. As an example, the incidence of Chronic Obstructive Pulmonary Disease (COPD) and other respiratory diseases is higher in metropolitan areas with high smog and poor air quality than it is in rural areas. In many countries, there are persistent racial disparities in health coverage, chronic health conditions, mental health, and mortality. The COVID-19 pandemic is further highlighting significant social boundaries and differences in access to, and quality of, care based upon race, resulting in poor outcomes in racially and ethnically diverse communities, especially in the United States.[7,8]

Need for Diversity and Inclusion

While the need to include diverse populations in randomised clinical trials is increasing, this also increases the legal responsibility of drug development companies to ensure patient care for diverse groups beyond the clinical trial care setting.9 Once patients are part of the drug treatment regimen delivered by the clinical trial, they have the right to continued care until the drug is available on the market, under the ethical guidelines of the World Medical Association's Declaration of Helsinki 2013 Article 34, which states,

In advance of a clinical trial, sponsors, researchers, and host country government should make provisions for post-trial access for all participants who still need a product identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.[10]

Unfortunately, this creates an inherent conflict between commercial focus, which may be on 'high reimbursement' countries (i.e., countries where patients can usually afford expensive treatments due to high levels of health insurance coverage), and patient care in emerging markets and Low- and Middle-Income Countries (LMICs), where health insurance reimbursement for drugs and care are more restricted or limited to government or single-payer care systems. We can take an example of targeting drugs for people of African descent in high reimbursement regions such as Western Europe and North America. To better understand genetic disease dependency by conducting trials on high numbers

of patients for statistical relevance, one would need recourse to larger populations in Western or Central Africa, where genetic ancestry can be traced. However, many African nations have low to moderate drug reimbursement compared to more developed nations and therefore the drug companies may be reluctant to site their trials there, as the principle of continuity of care would insist on them continuing to provide the same drugs to the trial participants even if they cannot be reimbursed.[11]

This is especially true for many genetically dependent rare diseases. The per capita diagnosis of many genetically rare diseases is higher in many emerging markets and LMICs than in developed countries, however the focus for many of the newer higher reimbursement gene therapies for rare disease is on high reimbursement markets, not on the populations in geographies most often in need.

Diversity has several different meanings and a wide context. In the United States, diversity in clinical trial recruitment is measured against US census diversity metrics. This is the classification used in the recent guidance by the Food and Drug Administration (FDA).[12] The problem is that US census classifications do not match global racial categories,[13] a point further developed in a paper on "race" definition recently published in JAMA.[14]

Applying US census race metrics globally ends up treating race generally and removing many racial and ethnic subgroups. Specifically, US census race metrics characterise race and ethnicity based upon where populations migrated or moved into the US from, not the actual ancestry of the populations.

For trials assessed by the FDA, the challenge is how, or if, this guidance can be translated to trials outside the USA, where racial diversity within populations is not defined the same way. For example, the category "Caucasian" has little to do with the countries of Georgia or Armenia, where the Caucasus mountains lie.

The category "Hispanic or Latino" does not refer to European Spaniards (who would be classified "White" under US census terms), but rather individuals with ancestry from the Caribbean, Mexico, Central America, and South America. In fact, Hispanic or Latino populations from North America, the Caribbean, Central and South American are often various mixtures of the original local indigenous pre-Columbian tribes with Europeans from Spain, as well as African slaves, and later further population migration from Europe and Asia.

Most African Americans have ancestral relatedness to slaves that were shipped from Western Africa, not only into America, but also the Caribbean islands and South America. However, genetically, these slaves were collected from at least four distinct West, West Central, Southwest, and Southeast African population groups, not a homogenous population. Today, many African Americans can trace their ancestry through genetic linkage to African, European, and Native American populations.[15,16]

The issue is that race and/or ethnicity are not always recorded in medical records in countries around the world. In fact, the EU General Data Protection Regulation (GDPR) explicitly prohibits collecting this information, even for clinical trials, unless explicitly justified and approved by the respective data protection authorities. As an example, in Poland, where a clinical trial enablement study was recently completed, the population diversity breakdown based upon US census data categorisation is as follows: the majority are White European, and locally of Eastern European origin, or Caucasian. In many countries within Clinerion's own global

US Census: Race Categories and Definitions
The minimum categories for data on race and ethnicity for Federal statistics, program administrative reporting, and civil rights compliance reporting are defined as follows:
-- **American Indian or Alaska Native.** A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.
-- **Asian.** A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.
-- **Black or African American.** A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
-- **Hispanic or Latino.** A person of Cuban, Mexican, Puerto Rican, Cuban, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."
-- **Native Hawaiian or Other Pacific Islander.** A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
-- **White.** A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Source: Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. Executive Office of the President, Office of Management and Budget. October 1997 (13)

network, race and ethnic data are captured when available, but are not always mandatory and therefore often incomplete. The question is how this diversity, if captured, overlaps with the FDA census categories, and thereby aids diversity from the perspective of US clinical trial diversity metrics.

This is important because the FDA is the world's largest medicine and medical device regulatory agency sheerly because of the size of the US healthcare market. Global healthcare projections for 2022 state that the US will be 42% of the global market, with Western Europe at 23% and Asia and Australasia at 24%.[17]

In the EU, the EMA ICH-E5: ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA regulations are focused on intrinsic and extrinsic ethnic factors that will impact the safety and efficacy of a medication in any of the ICH member and observer countries.[18] Essentially, intrinsic, and extrinsic factors model nurture (associated with environment or cultures) versus nature (associated with genetic polymorphism, age, gender, sex, body mass and other physical metrics). The intent of the ICH-E5 regulations (released in 1998) was to incorporate targeted foreign population diversity into trial design to include sufficient test metrics to validate safety and efficacy in specific countries. The regulation's Appendix C highlights 3 major ethnic groups within founding ICH regulatory (Japan, US, and EU) members, Asian, Black, and Caucasian) and treats EU countries as ethnically Caucasian, but reviews differential ethnic diversity in the other countries where approval is requested. In summary, the EMA, in accepting foreign

Country	Activated Sites
Argentina	1
Australia	19
Austria	2
Belgium	8
Bulgaria	4
Canada	7
Croatia	4
Czech Republic	5
France	24
Georgia	3
Germany	26
Greece	5
Hong Kong	4
Hungary	8
Iceland	1
India	50
Ireland	5
Israel	12
Italy	13
Japan	50
Malaysia	7

Country	Activated Sites
Mexico	1
Netherlands	9
New Zealand	7
Norway	1
Poland	25
Portugal	8
Romania	11
Russian Federation	14
Serbia	5
Singapore	5
Slovakia	5
South Africa	3
South Korea	12
Spain	15
Sri Lanka	4
Sweden	2
Switzerland	2
Taiwan	12
Ukraine	17
United Kingdom	16
United States	100

Example showing global site diversity for trial: Gilead diversity Crohn's disease trial sites[20]

data for drug approval, also reviews ethnic population impact in the countries submitted for safe and efficacious use to harmonize approval and drug medication use when possible. Although not as ethnically explicit as the more recent FDA advisory guidance, the EMA guidance does represent broad ethnic groups and country/member population inclusion for clinical research and trial inclusion.[19]

Diversity Means Inclusion

One approach toward achieving diversity would be to include diverse populations and as well as diverse geographies that insure diverse genetic population inclusion. From an industry perspective, there is value in sponsors developing the diversity of sites globally, as it helps to gain regulatory approval by addressing race and ethnic diversity, if not through direct race and ethnicity identification, then through inclusion of diverse populations, geographically. Sites external to the US can lend intelligence on populations originating from Europe, Africa, Asia, and Polynesia. Although it is hard to trace exact pharmacogenomic phenotypes within diverse populations, broad sampling is critical as the next step forward to understanding healthcare, safety, and efficacy.

Lastly, the increase of decentralised clinical trials (DCTs) due to technological advances and the pressures of the COVID pandemic offers an encouraging trend to support clinical trial recruitment diversity. Individuals and populations who previously did not (or could not) have access to centralised trial sites now have more options to participate in trials. This offers local alternatives to patients, wherever they are in the world, to join trials they would otherwise be restricted from, due to access, transportation, work, social or other physical and economic limitations. The potential benefits of remote patient center trial management were recently highlighted in a report[21] on a recent Janssen study based upon a remote patient center trial structure.[22,23]

Conclusion

Genetics are increasingly part of not only disease treatment, but also response to treatment. Understanding and representing genetic diversity, not just population diversity, is therefore increasingly needed in clinical trials. Understanding genetic contribution to disease, as well as incidence of disease – because of location, race, social status, and proximity to care – are important aspects for diverse patient recruiting in clinical trials. The approach to diversity that focuses only on finding diverse populations based upon US census metrics is not sufficient. Census metrics do not represent genetic background, and US trials often do not recruit a sufficiently diverse population to represent global patient populations. The only mechanism to ensuring diversity is to include not just distinct ethnic groups, but also diverse global trial sites that ensure the inclusion of diverse genetic populations in trials. Additionally, the capabilities of DCTs will also enable broader social economic patient inclusion by bringing the trial treatment and data collection to the patient rather than requiring patients to always attend a centralized RCT site.

It is a small world, after all.

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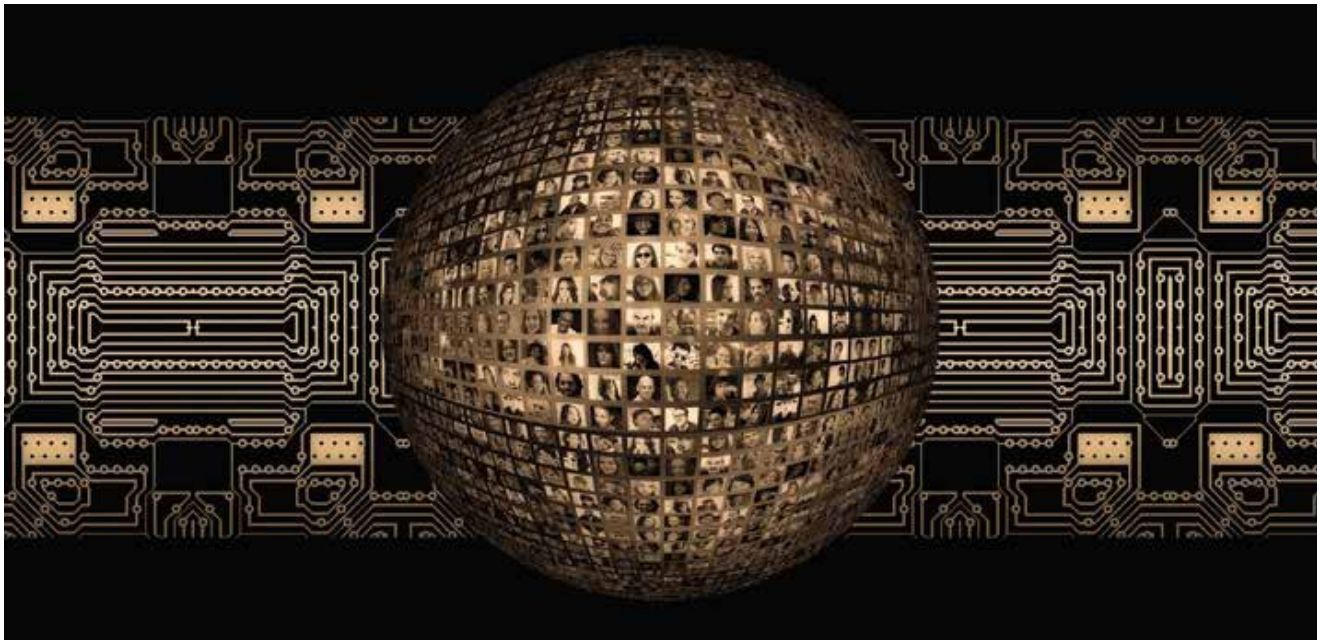

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