Increasing Diversity In Clinical Trials

Reducing drug development costs by 4.2% and increasing accessibility for ethnic minorities through virtual trials

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Executive Summary

Problem

A lack of participant ethnic diversity during earlier trials causes 20% of phase 3 failures.

50% of clinical trials are performed in just 1-2% of zip codes, most of which are higher-income areas. Given that 70% of low-income people in the U.S. are minorities there will be less diversity in the higher-income neighborhoods. This lack of diversity allows drugs with side effects affecting specific ethnicities to pass through first and second phase trials.

Solution

Building a virtual trial app to increase the diversity of trials by minimizing the barrier of travel.

Benchsci will build an app which facilitates virtual trials, expanding the available geographic range from which researchers can recruit participants. Benchsci will also build an app that searches through pre-existing data to predict which a drug's ethnicity-specific responses. This will allow researchers to target specific at-risk ethnicities.

Outcome

Finding adverse side effects in minority participants prior to phase 3 can reduce drug development costs by up to 4.2%.

By predicting ethnicity-specific responses to novel drugs, Benchsci will be able to help researchers to target specific ethnic groups. We predict that up to **20%** of phase three failures will be detected during the second phase, minimizing unnecessary phase three trials and reducing the development cost per new drug by **4.2%**.

Current Problems With Clinical Trials

Insufficient Trial Diversity

A lack of diversity creates 20% of phase 3 failures

Insufficient diversity in clinical trials refers to when a population is not proportionally represented by the participants of clinical trials.

Results of insufficient diversity

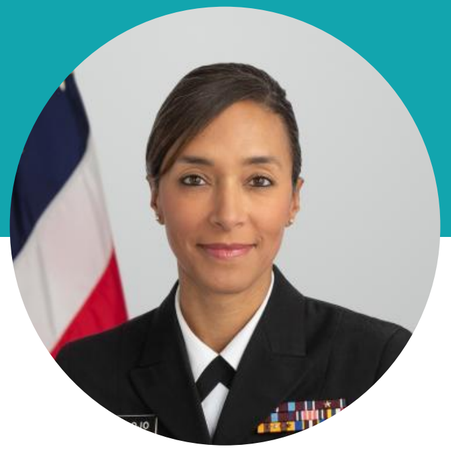
Insufficient trial diversity can result in adverse ethnic-specific side effects remaining unobserved during first and second phases. Because of insufficient trials diversity in the United States, 20% of molecular entities approved by the FDA have adverse reactions in ethnic minorities, meaning that they should have failed in phase 3 at the latest.

Scope of this problem

An analysis of clinical trials in the U.S taking place over 17 years showed that African Americans accounted for just 1.8-3.5% of participants. Asians and Hispanics also accounted for proportionally low numbers of participants at 0-7% and 1.4-3.4% respectively.

Importance Of Diverse Trials

The effects of ethnic-specific negative reactions



Richardae Araojo

FDA Associate Commissioner for Minority Health and Director of the Office of Minority Health and Health Equity (OMHHE)

Racial and ethnic minority participation helps researchers find better treatments and better ways to fight diseases that disproportionately impact diverse communities. In addition, it uncovers differences by race and ethnicity that may be important for the safe and effective use of therapies.

Reduced ACE response

Africans display a reduced response to ACE inhibitors. This lower response prompted the FDA to approve the combination drugs isosorbide dinitrate and hydralazine specifically for African American patients.

G6PD deficiency

G6PD deficiencies, most common in Africans and Mediterraneans, is a race-specific medicinal response. This response presents a high risk to these individuals when they are exposed to medications including sulfa drugs, anti malaria medication, and aspirin.

AstraZeneca Lawsuit

Effects of a trial lacking diversity

In 2003 Crestor, a statin created by AstraZeneca, was approved by the FDA. Crestor became a popular drug used alongside dieting and exercise to alleviate bad cholesterol. Crestor was also prescribed to slow plaque buildup and prevent heart problems.

Issue

One year after being approved by the FDA, Crestor's creators were required to update their drugs packaging to include dosage instructions for people of Asian decent. This was due to a previously unknown ethnic-specific risk of developing Rhabdomyolysis, causing muscle breakdown kidney failure, and possible death.

Consequences

Users of Crestor filed over 1,200 lawsuits in the state of California alone. This resulted in AstraZeneca fighting a legal battle for 14 years, eventually settling for $110 million in 2018.

$110 M

in settlement costs

Burden Of Travel

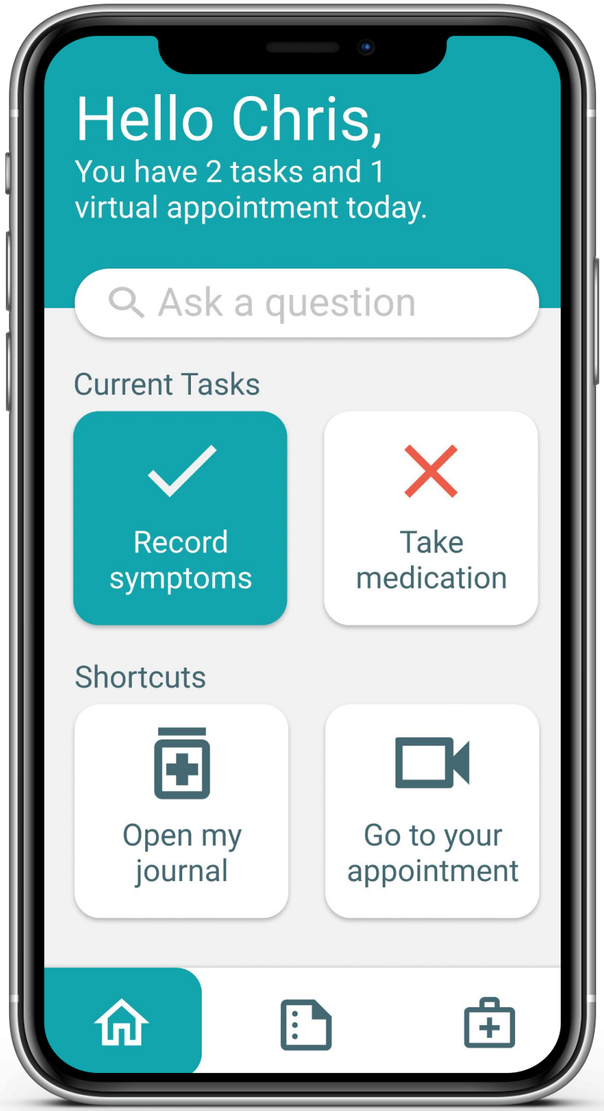
Barriers to ethnically diverse clinical trials

Participation rates for ethnic minorities in clinical trials are proportionally lower than expected. The most significant root cause of this problem is a high burden of travel.

High burden of travel

50% of FDA clinical trials in the United States are conducted in just 1-2% of zip codes. This affects a trial's ethnic diversity because the majority of these zip codes are those which surround hospitals and research institutes, thus they are in higher-income areas. Lower-income people, 70% of which are minorities, have therefore a farther distance to travel. In a study conducted in 2018 it was found that while higher-income participants traveled an average of 17.8 miles to participate in clinical trials, lower-income patients traveled over 58 miles. This increased travel distance has been strongly correlated with lower participation rates.

Solutions to Increase Diversity



Virtual Clinical Trials

Minimizing the need for travel to increase trial accessibility for underrepresented groups

Virtual trials are a method of conducting clinical trials through an app on the participant's phone. This helps people to participate in clinical trials without commuting to a clinic for daily or weekly check-ups. While not applicable in the first phase, virtual trials have shown promising results when used in phases 2-4. Virtual trials have also been shown to increase recruitment speed by four times, improving patient compliance by 33%, and decrease dropout rates by 20% when compared to traditional clinical trials.

Solving our root cause

Currently patients from lower-income areas travel a median 58.3 miles compared with 17.8 miles for patients from high income areas. By using virtual clinical trials researchers will be able to recruit participants from a much larger geographic area. When removing the burden of travel participants have been shown to be much more willing to participate in clinical trials. Thus, having access to this larger geographic area will increase the pool of potential participants and increase trial diversity

Secondary Virtual Trial Benefits

Improving patient compliance by 33% and patient retention by 20% using the Benchsci app

Digital journals

By using digital journals instead of traditional paper ones, clinical trials can increase journaling compliance from 11% to 94%.

Patient retention

Virtual trials have been shown to increase patient retention by 20%.

Compliance to protocol

By using a virtual trial researchers see an average compliance improvement of 33%.

Enrollment time

Virtual trials on average have four times faster enrollment per complete study when compared to traditional clinical trials. In some case this means saving up to 25% of recruitment budget.

Virtual Trial Limitations

Necessary considerations before moving forward

Not fully remote

Despite generally being completely remote, virtual trials will occasionally require patients to visit the clinic. This might occur for a variety of reasons including unexpected side effects, patient concerns, or state laws. Because of this all participants must be within a reasonable distance of the clinical trial.

Privacy

Federal and state privacy law such as HIPAA place strict guidelines on how private companies can use the healthcare data of an individual. Special provisions may be required in order to comply with these laws, including limitations on the kinds of data which can be collected.

Unique state laws

Federal and state laws surrounding the transportation and distribution of drugs is a factor that must be considered before researchers can use virtual trials. This will impact our product's reach as it will affect which researchers can and cannot use this product.

Predicting Side Effects

Using NLP to predict ethnic-specific side effects

By using Benchsci's pre-existing NLP technologies a model can be made which searches through published research for differing ethnic responses to drugs. This data can then be used to predict ethnic-specific side effects for novel treatments. This will help researchers to focus their recruitment strategies on the populations who are most at-risk for ethnic-specific reactions.

Available Resources

Studies such as the African Genome Project are in the process of documenting the genetic variation of people from continental Africa. Furthermore, public resources including OpenFDA contain repositories of side effects correlated with non-identifiable patient information.

Current Solutions

ADRtarget is an open-source machine learning program which predicts a drug's adverse side effects. The model analysis in-vitro data to predict a drugs reaction in-vivo. While more development would be required for our specific use-case this shows a promising first step.

AstraZeneca Case Study

How our solution would have saved AstraZeneca $110 million

In 2003 a statin created by AstraZeneca was approved by the FDA. While unknown at the time, this drug created complications in people of Asian decent. Missing this ethnic-specific side effect cost the company over $110 million. By using our solution AstraZeneca could have avoided this incident.

Implementation

In the development of Crestor, AstraZeneca would have used Benchsci's NLP models to predict ethnic-specific side effects. This search would have returned a strong possibility of Rhabdomyolysis in people of Asian decent. This would have been triggered by a differences in how Asians metabolise statins and how the statins change the body's pharmacodynamic properties. After learning of this, AstraZeneca would have specifically targeted Asian participants. This would drastically increase the chances of side effects being found in phase two or three trials.

Results

By using our technology AstraZeneca would have likely discovered the Asian-specific side effects in the second phase of their clinical trials. This would have saved their company **$110 million** in settlement and **fourteen years of legal fees**.

Implementation

BenchSci’s First Steps

Predicting adverse reactions

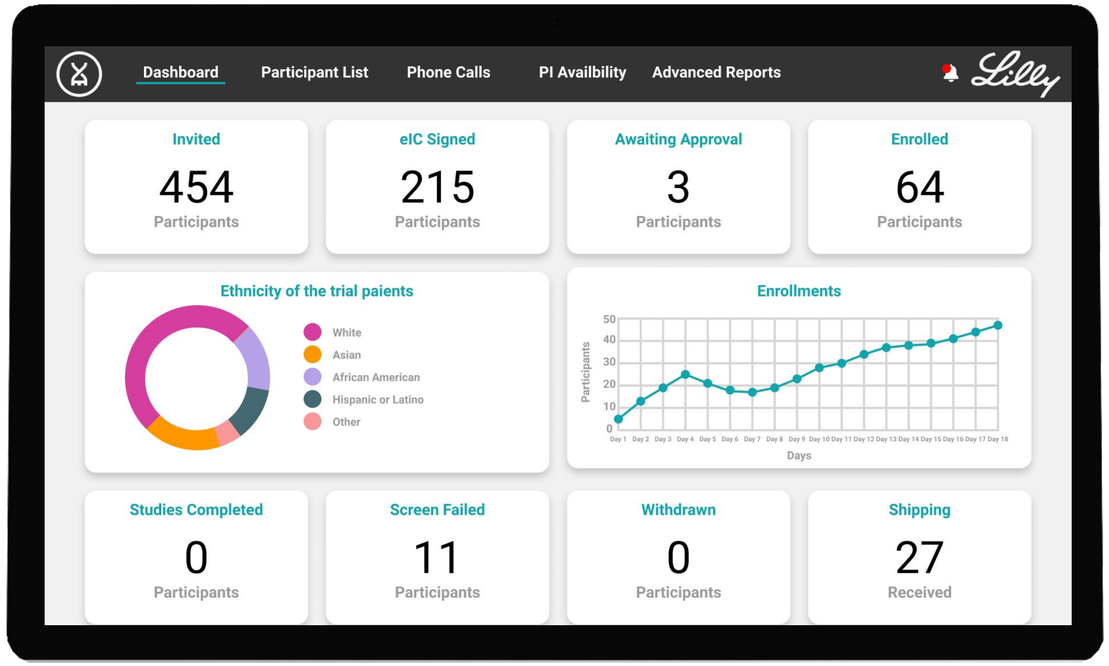
Benchsci’s currently ML models can be expanded upon to search for ethnicity-specific adverse reactions. Using this data a new model can be trained based on ADRtarget’s architecture which is able to predict ethnic-specific side effects given a novel drug. This tool can then be used to advise researchers on the diversity of their trials.

Building a virtual trial app

Building an app which enables one to conduct virtual trials will allow researchers to more effectively recruit ethnicities recommended by your predictive model.

Partnership with Eli Lilly

We recommend initially partnering with Eli Lilly to confirm the functionality of this recommendation. Eli Lilly has shown past interest in virtual trials but has not yet partnered with any other companies. Eli lilly is also currently partnered with your company for pre-clinical trials. This partnership would act as a showcase to other pharmaceutical companies on the effectiveness of this product.



Outcome

Saving 4.2% On Drug Development Costs

Breaking down the costs of clinical trials by phase in millions

Trial Phase	Phase 1	Phase 2	Phase 3	Overall
Cost of a clinical trial	$3.36	$13.56	$21.80	$38.72
Numbers of trials to create a drug	17.32	12.12	4.00	1.00
Cost of drug development	$58.22	$164.42	$87.22	$309.86
Number of trials that failed by phase per new drug	5.20	8.12	3.00	16.32 failures
Cost of failure by phase	$17.47	$137.47	$116.20	$271.13
Money saved if we stop 20% of phase 3 failures (due to diversity)	N/A	N/A	$13.1	$13.1

Note: from the paper we determined that the price to create a new drug including all trial failures is $309.86m.

On A More Personal Note

Thank you for providing us the opportunity to contribute to Benchsci and the goal that it stands for. Through this experience, we have all learned an incredible amount about artificial intelligence, biology, and teamwork, skill sets that will serve us well into the future.

We hope our recommendation is impactful to BenchSci's future direction, and that the platform grows to help more scientists find the what they need to succeed. One day, when we too need information to complete our clinical trials, we would love to use Benchsci on our devices.

Once again, thank you!

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