Challenges and Opportunities in Modernizing Clinical Trial Recruitment

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Abstract: Clinical trial recruitment is ripe for innovation. The current model is costly, often results in poor recruitment and offers inequitable access. To improve this system, we envision a peer-to-peer blockchain platform where patients control the depth and breadth of how their medical information is shared.

Clinical trials are an engine of scientific progress, responsible for ushering in a wide range of medical advances, from cancer therapies to innovative surgeries to COVID-19 vaccinations. Despite their crucial role in establishing the efficacy of new treatments, clinical trials are often delayed or abandoned due to difficulty with subject recruitment. Around half of clinical trials are delayed due to poor recruitment, with an estimated 80 percent of trials delayed for more than a month.[1] Additionally, many trials fail to meet their recruitment targets, potentially leading to underpowered, inconclusive study results. A survey of cancer studies by Bennette and colleagues found that 18 percent of clinical trials fail to enroll even half of their intended target.[2] Complex eligibility requirements, low prevalence of the studied disease, and competition with other clinical trials hamper enrollment. Moreover, clinical trials are often centered in large urban academic institutions with limited access to poorer, more rural, and ethnically diverse populations.[3]

The innovations of the recent decades and technological advances seen elsewhere in healthcare have set the stage for major disruption to the current model of trial recruitment. One such disruption could include a peer-to-peer platform for facilitating data exchanges that will fundamentally change the model under which trial recruitment is conducted on a global stage. Undoubtedly opportunities and challenges will be created because of this disruption. After describing the current model of clinical trial recruitment in Part I, we will describe this disruptive model in Part II, along with some of the potential benefits and challenges of such

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a model in Part III , focusing specifically on concerns relating to privacy and differential compensation.

Part I

Current Model of Clinical Trial Recruitment

Pursuant to the current model of clinical trial recruitment, a sponsor (either industry or academia) engages principal investigators at multiple sites, many of whom are located at academic institutions. These clinical sites are then responsible for recruiting their quota of the total trial population using methods including leveraging their existing patient registries, engaging network providers to refer patients, and advertising in the community. The sponsor, or more often a third-party delegate of the sponsor, may run their own parallel advertising efforts through TV, radio, billboards, or social media. Once a potential study subject is found, they are typically referred to a study coordinator who performs an initial screening for eligibility, consents the patient to share their data, and begins formal screening.

The current recruitment model depends on the breadth and depth of each principal investigator's database and referral network. These data silos of patient information are rarely shared between clinical trial sites, limiting a trial's recruitment pool to the fraction of the total patient population known to the sites enrolled in a clinical trial. This can especially hamper recruitment of trials on rare conditions, where the baseline low disease prevalence is already a barrier to adequate enrollment. Moreover, the sharing of potential patient data between institutions can be impeded by multiple clinical trials at these institutions competing for the same patient population.[4]

Likewise, it is difficult for patients to know they are eligible for clinical trials. For instance, a patient traveling to a tertiary referral center interested in being part of a clinical trial is limited to the set of studies that particular institution is participating in. Patients who lack access or the means to travel to a tertiary referral center are even less likely to be referred to a clinical trial. While most clinical trials in cancer have been conducted at large academic medical centers, 85 percent of cancer patients are diagnosed and treated at local community practices.[5] The differential is even starker for rural compared to urban community practices. One survey found that rural patients were 77 percent less likely to receive an invitation to a clinical trial than their urban counterparts.[6] This disparity might help explain higher cancer mortality rates in rural populations.[7] Recent efforts to combat a lack of access have included providing searchable trial databases such as Power or clinicaltrials.gov.[8] However, these patient-facing efforts can be difficult for the average patient to navigate and determine their eligibility for a specific trial.

Ultimately, the limitations of the current system mean that patients that could benefit from clinical trials are not being enrolled and similarly clinical trials are not benefiting due to the lack of their enrollment. Only an estimated 2-5 percent of adult cancer patients participate in a clinical trial.[9] Those who do are significantly less likely to represent racial and ethnic minorities disproportionally affected by those same cancers. For example, while Black Americans experience the highest cancer incidence rates, their participation in clinical trials lags behind all other major ethnic groups. Many barriers, such as decreased likelihood of physician referral, historical distrust of clinical trials,

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costs, and inadequate transportation, play a role in this enrollment disparity. Moreover, studies demonstrate that minority populations have less awareness of the availability of clinical trials despite equal willingness to participate.[10]

These disparities in clinical trial representation limit the generalizability of clinical trial results as all too often the study population does not match the wider population. The current system also ensures that the benefits of clinical trial participation are not shared equally. For instance, despite the benefits of participation being incidental rather than direct, patients enrolled in cancer clinical trials have lower mortality rates for lung, breast, and colon cancer.[11] Additionally, therapeutically significant population-specific pharmacogenomics profiles or receptor expression patterns may be missed if these populations are underrepresented in trials. Inequity in trial recruitment has long been recognized as a barrier, and the National Institutes of Health (NIH) Revitalization Act of 1993 was, in part, passed to address this equity gap.[12] The Act mandated increased enrollment of women and minorities and prohibited using cost as a reason for their exclusion in NIH-funded research.[13] Despite some improvements, nearly 30 years since the Act's passing, these populations remain underrepresented, and many trials still fail to adequately report trial composition and outcomes by race.[14] Other efforts such as the *All of Us* Research Program in the US have tried to build a more diverse heath database but such attempts lack specificity and flexibility. The current clinical trial recruitment and enrollment system is ripe for innovation and wholesale change.

Part II: Flipped Recruitment Model

The COVID-19 pandemic, in many ways, catalyzed disruptive innovations within clinical trials and clinical trial recruitment. For example, because of restrictions associated with the pandemic, interest and implementation of decentralized clinical trials (DCTs), which are trials characterized by less dependence on traditional research facilities or other intermediaries, were vastly increased. Although the acute need to urgently disrupt the current model of clinical trial recruitment in the setting of unprecedented challenges brought on by the pandemic has subsided, it is anticipated that this trend of disruption will continue in the coming years.[15] With ongoing advances in technology such as blockchain, artificial intelligence, Web 3.0, and the Internet of Medical Things (IoMT, which generally refers to a network of internet-connected medical devices, including software, that connect with healthcare information technology systems), the stage is set for further and more significant disruptions in clinical trial recruitment.

In the not-too-distant future, it is easy to envision a world where data collection and sharing will become ubiquitous and independent of political and institutional boundaries. In this future, potential subjects will have full access to their data as well as full control over how it is shared.[16] This contrasts with today's model, where even though patients in most jurisdictions have a legal right to access their personal data, they do not have ownership over their actual records. Therefore, their data can only be accessed through a third party (e.g., health systems).[17]

This envisioned future could lead to a "flipped recruitment model" where, instead of potential subjects and their care team identifying and providing referrals to trials, these subjects are empowered to advertise more actively to the entire pool of potentially interested investigators. In turn, the power structure will shift from recruiters and other intermediaries back to the potential subjects. Moreover, as the role of intermediaries is reduced, this model will likely decrease the overall costs of clinical trial recruitment and increase opportunities for eligible subjects by increasing the pool of potential studies.

The platform for such a model could use blockchain technology to allow for decentralized data where subjects have greater control over the depth of what is shared and the breadth with whom it is shared. Utilizing cryptographic elements of blockchain technologies, subjects could have complete control over their data. Under this new model, potential subjects can elect to avail their deidentified (or identifiable) data on platform(s) where it can be searched by recruiters allowing for a true direct-to-participant recruitment model. Such a platform could provide various incentives to encourage data maintenance and sharing by potential participants as well as health systems.[18] Investigators will in turn be able to access patient populations that previously were unavailable to them. Clinical trials, as a result, will be more likely to match the general population in terms of ethnicity, socioeconomic status, rural vs. urban, and other recruitment factors currently causing inequity in clinical trials. Additionally, participation by smaller (or less funded) health systems, including community practices as well as international institutions, will be more likely, as access to a large volume of patient data will not be a prerequisite to enrolling as an investigator in a trial. The flipped model would also be able to speed up recruitment by allowing investigators to have upfront data for eligibility

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determination, helping to eliminate screening failures which add substantial cost to a trial and delay its recruitment phase.

Such a disruptive model will undoubtedly create numerous challenges and opportunities which are beyond the scope of this manuscript. Some of these are created due to the inherent nature of the disruption, while others are created by a system that transcends political borders but must still operate within the confines of national law. Moreover, digital illiteracy and cost are certainly barriers that must be overcome if such a system is to become operational. However, none of these are insurmountable.

Below, we focus on two specific opportunities and challenges afforded by this flipped recruitment model, (1) privacy and (2) differential compensation. We are hopeful that this paper will spark further interest in the topic and serve as a catalyst for further research into the other relevant challenges and opportunities of this novel model.

Part III: Ethical Challenges and Benefits of the Flipped Model

Privacy

The prospect of a data marketplace between prospective subjects and study sponsors holds great promise in speeding clinical trial recruitment and achieving more equitable access to clinical trials. However, by increasing access to data and changing how that data is shared, a flipped recruitment model invites both privacy challenges and potential benefits. Health records contain a trove of information that patients might want to keep private. With recent advances in health data technology, the amount of data contained within health records will exponentially increase in the coming years. Some have argued that the need for privacy is innate and influenced by the potential for information to negatively affect rights, privileges, and standing in society.[19] Such information may include decisions concerning cosmetic surgery, psychiatric services, substance misuse disorder, chronic illness, genetic conditions, reproduction, and many others. Therefore, ensuring privacy is essential in any future recruitment system, from a legal and ethical standpoint. Studies have shown that the perception of privacy risk and trust in the system will directly affect willingness to participate.[20] Consequently, even absent legal and ethical concerns, building trust will be paramount in maximizing participation by potential subjects and creating a functional platform.

Under the current system, multiple stakeholders, including study sites, trial sponsors, and subjects are independently responsible for data stewardship. This introduces multiple potential points of failure; one healthcare system data breach threatens to expose large amounts of protected health information (PHI). Unfortunately, healthcare data breaches have only become more common in the era of electronic health records, increased data capture from the IoMT, and patient mobile access to online health services.[21] Just in the US, the number of data breaches of 500 or more records increased from 199 in 2010 to 714 in 2021. Over 113 million individual records were exposed in 2015 alone.[22] Breaches commonly occur due to hacking, unauthorized internal disclosures, or theft/loss of data.[23]

On average, a data breach costs a healthcare institution US$6.45 million globally and US$15 million in the United States.[24] While this represents a substantial and potentially harmful cost, it also provides a powerful incentive for continued organizational innovation to prevent future breaches. The current recruitment model places the responsibility for privacy on each organization that has access to PHI. A flipped recruitment model, without a centralized organization accountable for patient privacy, would have no such incentive if a data breach did occur. One remedy, requiring international collaboration, would be establishing a governing body that oversees system vulnerabilities and establishes protocols and standards that make structural failures less likely. The approach would be similar to the role the World Wide Web Consortium (W3C) and Internet Corporation for Assigned Names and Numbers (ICANN) play in ensuring the smooth functioning of the internet.[25] Funding and membership of this governing body could be provided by the same study sponsors the new recruitment system stands to benefit. It would also be beneficial to have independent and unbiased members on this governing body, potentially appointed by participating governments. Data breaches would be less likely given the distributed encrypted nature of data in our model. However, were they to occur, financial risk could be shared proportionately among the users of the system, providing additional incentives to act collectively to protect subject privacy.

The model proposed above would also be faced with the challenge of remaining nimble on the global scale while navigating a complex web of individual countries' privacy laws. Beyond the Health Insurance Portability and Accountability Act (HIPAA) in the United States, any functioning global recruitment system would also have to ensure compliance with the General Data Protection Regulation (GDPR) in the European Union, the Personal Data Protection Bill (PDPB) in India, and the Personal Information Protection Act

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in South Korea, to name just a few of the applicable sovereign patient privacy regulations. Countries such as Germany make compliance even more difficult by layering additional regulations on top of regional standards like the GDPR.[26] Devising a system that adheres to all of these regulations across the platform would be impractical from a design standpoint and likely unusable from a user perspective. Therefore, this necessitates moving beyond a national approach to privacy and adoption of an international standard. Conversely, a decentralized platform would struggle to be compliant without the benefit of central governance and accountability. To bridge this gap, a flipped recruitment model would require a central governing body to ensure continued adherence to applicable laws.

Though a flipped recruitment model would still be prone to privacy concerns, it could offer increased security compared to current data protection standards in healthcare. Whereas existing electronic health records (EHR) are maintained on centralized servers, our model would allow potential subjects to provide data using encrypted blockchain technology that does not require a central data repository. Instead, data is distributed as a series of encrypted nodes recorded on a public ledger with built-in redundancy and immutability.[27] Access is limited to those with proper permissions, and potential subjects could limit the amount of data viewable to each user. For example, a subject could make their complete data viewable to a healthcare system they trust while allowing only their surface demographic data to be searchable by other institutions.[28] This is superior to the current model, which does not allow gradation regarding how much data is shared, and ultimate control and ownership remain with the institution. Control in this new system depends on a subject keeping their encryption key secure. Phishing attacks and subject device vulnerabilities could compromise access to this key; however, this kind of data breach would be limited to one individual rather than numerous subjects within an institution, as is the case in the current model. Therefore, the decentralized nature of the system will limit any potential gains from the breach and serve as yet another notable disincentive for malicious attacks. This alone should outweigh any increased risk of data breaches and privacy vulnerabilities for those with limited access or literacy in information technology in the absence of large institutional informational technology infrastructure. From the subject's perspective, it is important to have safeguards in place to at minimum provide a mechanism for data recovery in case there is a loss of an individual's encryption key.

Differential Compensation

The level of data granularity in this new recruitment model will allow for a more targeted selection of research subjects which could, in turn, strengthen the case for differential compensation to subjects based on their individual value to a given trial. The added value can be from a rarer characteristic (e.g., gene, disease, race, etc.), geographic location, participant's effort in updating and maintaining data, or any other variable. However, this challenges the current ethical framework surrounding payments to clinical trial subjects that would need to be addressed in anticipation of this paradigm shift.

To improve recruitment, study sponsors typically employ financial incentives to increase the size of the recruitment pool. Incentives can include travel-related reimbursement, compensation for time spent, or standalone financial incentives. In its guidance, the FDA notes that paying subjects for their participation is acceptable and should be done justly and fairly.[29] The agency discourages a level of payment that presents undue influence or coercion on a subject's decision to participate. The institutional review boards (IRBs) responsible for approving clinical trial protocols usually stipulate that a trial provide the same incentives to all patients as a matter of equity.[30]

While IRBs have historically allowed investigators to offer different compensation at the site level based on local wages and purchasing power parity, similar discretion in compensation has not been extended to the individual subject level. Indeed, the Secretary's Advisory Committee on Human Research Protections (SACHRP), the governmental committee responsible for safeguarding research participants in the US, discourages such differential compensation. It views such an approach as a violation of the principle of equitable compensation for equivalent sacrifice and prefer a model that prioritizes equity over true compensation. Moreover, SACHRP's guidance classifies additional incentive payments to hasten study enrollment as a potentially problematic source of undue influence.[31]

Under our proposed flipped recruitment model, one could easily envision a situation where trials can become quite selective in recruiting participants and target potential subjects based on their specific characteristics (e.g., gene, disease, race, etc.). Depending on the rarity of these characteristics, the "added value" that each participant brings to the trial is unequal. In some instances, the inequality of the added value may only be marginal, while in others, it can be of tremendous value. Then why, from an equity standpoint, should trial participants be compensated equally, espe-

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cially when the added value of a specific subject for whatever reason is not trivial? The same philosophical approach can also be applied to other individual-level differentiators, such as geographical location or the effort required to update and maintain data.

The broad concept of differential compensation for research participants and basing such payments on market-driven rates such as added value are not novel. Other scholars have previously explored various models and their ethical implications. For instance, under one such framework for differential compensation proposed by Persad and colleagues, the legitimacy of compensation for unique values added by a specific participant is recognized. However, they see differential compensation based on the research participant's value to the trial as ethically optional. They argue that prospectively (or even retrospectively) determining the value of a specific participant's contribution may be difficult and raise ethical aversion to payment for features not within the subject's control (e.g., skills or effort which can be controlled by a participant compared to a participant's genes which is outside of their control).[32]

Under a flipped recruitment model, a stronger case for making such payments obligatory is created given the level of detail available to recruiters at the time of recruitment and the selectivity afforded to them. Persad and colleagues have raised concerns regarding obligatory differential compensation when determining the true value of a subject's contribution is difficult. However, simply because, in some cases, it might be more challenging to identify the exact value of a subject's contribution, this should not deter compensation in cases where it is readily identifiable. Moreover, in other types of economic activity, decisions on price and compensation are often based on the payee's perceived value based on need and scarcity at the time of need (*ex-ante*), which may differ significantly from the real value. In this regard, clinical trial subject recruitment should be no different. Therefore, even in cases where prospective assessment may be difficult, it would be ethical to compensate subjects based on the perceived added value of their unique characteristic. Another objection to differential compensation is the risk of rewarding subjects based on their "luck," defined as having a sought-after characteristic without any effort by the subject.[33] In many ways, this so-called "luck" is the basis for which trial subjects are recruited and compensated in the first place. Therefore, it is difficult to argue that it should be excluded as part of determining differential compensation.

Others have further advanced this line of thinking to include various other market forces in addition to the "special/unique value" of the specific subject as the basis for compensation, noting that offering differential compensation does not violate requirements of justice as ultimately it is designed to help the study meet its scientific and social goals.[34] Continuation of this framework will naturally lead to concluding that research subjects must be compensated differently based on their varying overall contribution to the underlying scientific and social goals.

Therefore, we see no ethical barrier in the underlying concept of differential compensation based on the value added by a subject to the trial. However, it must be ensured that the prospective assessment is made in good faith and based on available scientific evidence.

Therefore, we see no ethical barrier in the underlying concept of differential compensation based on the value added by a subject to the trial. However, it must be ensured that the prospective assessment is made in good faith and based on available scientific evidence. This includes ensuring participants are compensated equitably given the inherent information asymmetry that exists between the trial sponsor and participants through prospective, IRB-approved methodology. In order to implement differential compensation, respective national and international ethics bodies must update their guidelines and ethics codes to prepare for the new paradigm.

Nonetheless, differential compensation models should not be such that the underlying ethical and legal underpinning of informed consent is violated, and usual safeguards must be in place. Namely, it should neither be coercive nor present undue influence.[35] This is especially important as it is likely that unique characteristics that form the basis of differential compensation may, in fact, place the subject in a disadvantaged population and, therefore, more vulnerable to coercion and undue influence. Moreover, under this model, the role of an independent referring

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provider is likely to be reduced. Consequently, opportunities to receive unbiased advice may be limited, further exacerbating vulnerabilities. Thus, IRBs should scrutinize these differential compensation schemes instead of a blanket rejection and a clear model delineated from the onset to ensure ethical and regulatory compliance.[36]

Conclusion

The current model of clinical trial recruitment has failed to fully realize the ultimate goals of clinical trials. Under the current model participation of many potential subjects is limited, costs are substantially increased, and results may not be generalizable to the general public while depriving potentially eligible and willing subjects from participating and benefiting from the trial. Technological advances in recent decades will likely lead to the disruption of the traditional model of trial recruitment by creating a flipped marketplace where the direct-to-participant recruitment model will be the default. With regards to privacy, there needs to be safeguards in place to ensure participant privacy and compliance with applicable laws. Furthermore, this new model will create an opportunity for the implementation of differential compensation which requires a paradigm shift from the current approach. Undoubtedly, other challenges and opportunities will arise under this new model that need to be addressed in the coming years including ensuring equitable access to the fruits of the clinical trials that can now more easily be conducted in poorer countries.

Note

The authors have no conflicts of interest to disclose.

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