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Ethical and Regulatory Considerations in Patient-to-Patient-Referral Recruitment Plans

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Recruitment into clinical studies is a key component to conducting safe and efficient research. However, recruiting patients is challenging and is often a tension point in the conduct of research. In this whitepaper we explore the power of "patient-to-patient" referral programs as a technique to overcome enrollment bottlenecks

The earliest phases of research often require the participation of healthy individuals, and this population can be difficult to reach. Additionally, some studies require more targeted patients due to the nature of the study population and this can make it difficult to identify and reach appropriate individuals who may qualify for the research. Often, the best person to encourage others to participate in research studies is someone who has had a positive experience as a research participant them self. Therefore, one of the recruitment strategies frequently employed to overcome recruitment hurdles is called patient-to-patient referral.

Patient-to-Patient Referral Programs

"Patient-to-patient" referral programs - which often refer to healthy volunteers rather than patients with a disease or condition - are generally designed to motivate someone who has had experience with being a research participant to reach out to their friends, family members, and other personal contacts. The experienced participant encourages others to either consider enrolling in a specific clinical study, or to consider research participation in general. To persuade them toward this outreach effort, researchers or research facilities provide a monetary reward to the referring person, usually for each contact who contacts the site about participation in a study. Many referral programs, especially for healthy volunteer research, are not for specific studies, but rather encourage others to join a database from which future studies can be recruited.

One specific type of patient-to-patient referral program is "snowball sampling", which is a non-probability sampling method in which a participant in the research study is asked to help recruit other participants by relaying information about the study to peers they know who are in the group being studied; for example, other people who are community leaders, other people living with long-term HIV, or other families where someone has a specific rare disease. Snowball sampling is frequently used in qualitative research, when the researchers are seeking a group with very

specific characteristics, and when people within that group are likely to know others within the group. Study populations obtained through snowball sampling techniques cannot be considered a random or representative sample of the population, so it is not appropriate for certain types of research and researchers must be aware of the potential for selection bias and the possible impact that may have on study conclusions. Snowball sampling would not be used for clinical trials for this reason, but may be used in observational biomedical research, such as when doing surveys of patients.

IRB Oversight of Patient-to-Patient Referral Programs

Any recruitment plans including potential participant referral programs must be submitted to the Institutional Review Board (IRB) in advance of beginning them, whether they are initiated at the start of the study or added later after the study has already begun. Any written materials, such as brochures prepared for current participants to distribute to others, content for them to share or post online, or scripts for them to use, must also be submitted to and approved by the IRB.

Benefits of Patient-to-Patient Referral Programs

Patient-to-patient recruitment can be particularly effective for harder to reach

populations, or to reach a population with uncommon characteristics.

The potential recruitment benefits of the strategy include:

- Participants are generally more apt to trust close, personal peers rather than individuals they do not know. The referring party can provide direct, trusted knowledge to the potential participant. The referring party can describe their experience and expand on information not directly discussed during the consent process. This may include realistic expectations regarding the necessary time commitment and experiences related to the specific research.

Examples of this include commuting time, parking availability, and office wait times.

- One participant may have relationships with several qualified individuals. For example, if the research involves a rare disease, a person involved with an advocacy group can provide information to the entire group via one social media post or discussion at an annual meeting.
- Participants can outreach to individuals who may not have the same access to information. Individuals frequently have access to different information compared to other people in their network, based on their socio-economic status, hobbies and interests, as well as access to healthcare providers. Patient referrals provide an opportunity to reach potential participants who may be missed by traditional recruitment campaigns.

Concerns

While patient referral methods can create new recruitment opportunities and the methods are not inherently problematic, they do raise some potential issues that need to be considered prior to setting up the program.

- Patient referrals may create a bias in the research due to having more similar participants than may naturally occur otherwise. Personal networks tend to be more analogous to the individual in terms of race, socioeconomic status, geographic location, etc., and patient referrals could bias the research by oversampling a particular group. Most research studies will have a limit to how many participants will be enrolled, and the use of patient referrals may lead to a situation where more similar participants are enrolled than may be the case without patient referrals. Even if this doesn't bias the study, it could distort the results and/or limit the applicability as there is not a more representative cross section of the population being enrolled into the research. Of course, if the goal of the referral program is specifically to enrich the study population for a certain type of participant, this may not be a concern.
- Research sites may want to have processes to handle situations where the referring party knowingly refers unqualified participants simply to increase their payment. Programs sometimes try to manage this by paying for referrals only if the referred person is eligible for and agrees to enroll in the study. However, this is not an appropriate control since the referring participant cannot control whether someone else meets all study eligibility. Paying a participant only if their referral agrees to be in the study can cause incentive for the participant to unduly influence the referred party to agree to participate. or to encourage them to lie about their eligibility for the study. It would be acceptable for the research site to put some restrictions on the referral program,

which could include a prescreening process to evaluate basic eligibility requirements such as appropriate age and condition, and restrictions on concurrent research participation. The site could also limit the number of referrals provided by each referring party. As many of these programs are used due to low recruitment or to increase pre-screening databases, this may not be an overly burdensome issue.

- Patient referral programs may include the possibility of coercion. Coercion is the act of persuading someone to do something, by threats or influence. For example, relationships between the referring party and the potential participant may include a power imbalance, where the potential participant is more likely to join the study or to stay in a study they would have otherwise withdrawn from simply so that the referring party gets paid.

Setting Up a Patient-to-Patient Recruitment Program

A well-designed patient-to-patient referral program should include:

- Payment to the referring party based on the referral, without requiring the potential participant to meet certain milestones such as randomization, length of participation, or completion of the study.
- Specificity about when the payment will be made. For example, the program may

require that the referring party receives payment after the potential participant sets up an appointment, or completes a screening visit, but the payment should not be contingent on actual enrollment or randomization of the potential participant in the study.

- Payment in an amount that is unlikely to provide an incentive for the referring party to pressure the potential participant to enroll in or stay in the research.

Individuals tend to trust the people they know and are more likely to do something if the suggestion comes from a family member, a friend, colleague, or even an acquaintance. Because of this, patient referral practices can be extremely effective. Patient referral programs have the potential to increase enrollment into research studies by allowing trusted individuals to share their knowledge and experiences with their friends and family members. Ideally, these strategies reach individuals who may not otherwise be aware of the research or may be hesitant to participate. When designing these programs, research sites should be aware of the factors that may create the potential for coercion or undue influence, bias the participant pool, or create a drain on staff resources.

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