Electronic Recruitment and Validation of Patients for Outcomes Research Studies in Rare Diseases: What Are the Potential Challenges?

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For outcomes research studies in rare diseases, validation (ie, verifying patients are really who they say they are) is even more important as patients likely need to have diagnosis of a specific condition and take a specific medication for a certain period of time.

Electronic recruitment and survey completion is a popular, cost-effective way to access hard-to-reach patient groups, particularly in rare disease outcomes research. These patients are often deeply engaged with online communities regarding their condition and treatment. Patients are usually eager to discuss and share their experiences, with the intention and hope that treatments and outcomes will improve because of their participation.

Good study design for data collection from patients with rare diseases requires careful planning of the electronic recruitment and validation process ahead of time. Validation of patients for inclusion in research studies can take many forms, but essentially refers to the process of verifying that patients are really who they say they are and that they are the type of patients required for that specific study. For outcomes research studies in rare diseases, validation is even more important as patients likely need to have diagnosis of a specific condition and take a specific medication, and have been doing so for a specific period.

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To achieve realistic targets and deliver accurate and reliable data, it is important to allow for a feasibility assessment that can help tailor the study recruitment and validation process. The study team should draw up the most appropriate recruitment strategy—one that would consider factors such as the patient audience, sample size, and level of validation required. Decisions made about validation should consider how the recruitment selection process impacts patient knowledge, honesty, and engagement.

Considerations for Sample Size and Incidence Rates

There are several challenges in recruiting large sample sizes for outcomes research studies in rare diseases. First and most obviously, patients are limited in number as incidence rates are usually very low in rare diseases, sometimes as low as 1 in 1 million people with the specific diagnosis within the general population. Often larger sample sizes are desirable to permit the use of inferential statistics and to provide more confidence overall in the conclusions drawn from the available data. To increase sample size, it might be advantageous to accept patients from sources with less-documented evidence.

Second, the way in which patients are engaged and validated as part of the study can influence whether a patient wants to take part in that study. An effective screener is needed that is tailored to the patient audience, with considerations for recruitment inclusion and exclusion criteria. The simpler the recruitment process and the less-restrictive the eligibility criteria, the easier it will be to recruit patients to a study and therefore achieve a greater sample size. However, some studies by design will necessitate more stringent eligibility criteria, which must be verified before a patient can be screened as eligible for the study. Nevertheless, a combination of recruitment techniques and available recruitment sources is more likely to result in a larger sample size.

Potential Sources for Electronic Patient Recruitment

Patients with rare diseases can be recruited for electronic studies from a variety of different sources, all of which have advantages and challenges as outlined in Table 1 on the following page. >

Table 1. Potential sources for electronic patient recruitment.

Recruitment Source	Advantages	Challenges
Clinical sites	Direct contact with physicians and patients allows recruitment with nearly 100% validation of eligibility.	High cost and longer timelines. Sometimes lack of willingness or engagement from sites, physicians, and patients to participate.
Physician referrals	Eligibility confirmed by a physician who can also engage the patient.	Difficult to get high numbers of patients. Depends on the country and regulations.
Patient associations	Patient associations will post information about the project and patients can register their interest in the study.	A lot depends on the patient association secretary/gatekeeper and whether they want to spend time and effort on the study.
Social media/internet support groups	Rare disease patients often use social media to help find information and support for their condition. This creates a direct link to the patient.	Need to engage patients individually. Work intensive. Low response rate. Often social media groups are closed and need administrator's permission to post.
Recruiter networks and databases	Databases of engaged patients who want to take part in studies.	The databases are not very big and can become out of date.
Patient panels	Can get high numbers of patients for rare diseases as a specialist panel has been built.	Panel owners may not reveal identity of panellists and cannot verify on telephone. Engagement may be low.
Consumer panels	Can have hundreds of thousands of panel members and therefore many rare patients.	Low engagement and inability to verify other than via general profiling.
Shared open survey links	Can get a lot of respondents quickly.	Cannot be certain that the respondents are who they say they are.

Levels of Patient Validation

The level of validation should be determined by the study design, patient population, and recruitment source. Different levels of electronic validation may be required to ensure that patients are those the study is recruiting. Recruitment through clinical sites and physician referrals may require less-formal validation, as patients are recruited from a more reliable data source, and there is opportunity for confirmation of disease and more accurate capture of specific treatment history. Recruitment through patient associations, patient recruitment networks, or social media support groups are other popular options. Patients who join these support groups are often heavily engaged in their condition and treatment, and as a result, are often knowledgeable enough to self-confirm their validation during the screening process.

In contrast, recruitment via patient and consumer panels might pose a challenge for electronic validation, as there is little guarantee of how familiar and knowledgeable patients are about their condition. For instance, this form of recruitment might be appropriate in a study with a simple selection criterion for patients with asthma but may not be suitable for recruitment of patients with an advanced-stage cancer who may not be knowledgeable enough to self-confirm their treatment efficacy. Finally, recruitment through open survey links—even if posted on patient association or community websites or blogs—is rarely a recommended option as there is no reliable way to validate who is responding to the survey link. If this is the only available method of recruitment, the process could benefit from a detailed electronic validation procedure and further engagement with the patients to ensure they are a good fit for the study.

Patient Knowledge

Patients may not always possess the required knowledge of their condition and treatment to self-assess their fit with the study validation criteria. Ideally, screeners should be designed and worded in a way that patients can understand and engage with the study. There are several ways in which the study team can support patients during this process while motivating their participation. For instance, it may be beneficial for the study team to help support patients with the interpretation of technical or complicated concepts during the validation process. This may help guide and further motivate patients to take part and share accurate information about their condition.

Some studies may require physician confirmation of disease or treatment. In these cases, the study might offer an additional incentive to patients for reaching out and acquiring confirmation of technical information from a physician. This process would rely on patients having access to their physicians in a timely manner during recruitment to gather the required information, but the process would inevitably produce more reliable data. However, it is worth bearing in mind that not all patients are willing to approach their physicians for this information, for various personal reasons. There is an important compromise between validation level and sample size. If a study requires physician confirmation of diagnosis, then the study may need to accept a lower sample size of patients than if self-confirmation of diagnosis by the patient is enough.

There should also be considerations for cultural differences among patients with rare diseases regarding disease awareness and knowledge. In English-speaking countries, patients are often engaged and knowledgeable about their condition, especially if there is opportunity for patients to select healthcare providers and treatments. This is perhaps less apparent in countries where patients are traditionally more likely to depend on their healthcare provider for information. Expending some effort in assessing the extent and reliability of patient knowledge for a given population may pay dividends in ensuring the accuracy of data obtained.

Patient Engagement

Some electronic recruitment techniques can result in patients being less engaged in the study design and process. For studies

that source recruitment through online consumer panels, it may be that the patient respondents are used to receiving several survey requests, and as a result may not be motivated or engaged enough to complete the survey with a great deal of attention. This can lead to low-quality data (eg, speeders, flat liners), which are indicators of low engagement from patients. The study team can overcome this to some extent by aiming to engage with interested patients, highlighting the importance and value of the study for the rare disease community, and supporting them with interpretation of technical or complicated concepts. Patients with rare diseases are often part of a highly engaged community who are motivated to increase disease awareness and help encourage the availability of treatments, and this alone could yield higher patient engagement.

Patient Honesty

Although rare, the risk of wrongful recruitment or dishonesty from the respondent's side becomes an issue when using online open survey links that do not involve human or profiling validation steps. This increases the chance of a "fake" patient being involved, who may not have a diagnosis of the rare disease in question but may be interested in the offered patient incentive. It is important that survey access is limited to those who already have been electronically validated at a basic level. The screener should act as a further validation step as well. This is particularly important for patients with rare diseases, as the incentive often needs to be attractive enough to maximize the sample size.

Summary

There are several challenges for electronic recruitment and validation of patients with rare diseases for outcomes research studies; however, several measures can be taken to improve study design for the rare disease population. Careful selection of electronic recruitment sources and techniques, a well-designed screener tailored to the study population, comprehensive checks of study data, and if possible, a confirmation of diagnosis by a physician can all increase validation and help achieve accurate, reliable data.

Additional information

The preceding article is based on a workshop given at ISPOR Europe 2018. To view the presentation, go to https://www.ispor.org/docs/default-source/presentations/90361pdf.pdf?sfvrsn=a49f7501_0. For more on ISPOR's Rare Diseases Special Interest Group, go to https://www.ispor.org/member-groups/special-interest-groups/rare-disease.