Real-World Studies Need Patients Too!
Unique Considerations for Patient Engagement and Retention

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Patient-centric methods and approaches are integral to the design and execution of both interventional and non-interventional studies.[1,2] From within the tightly controlled clinical trial environment to the real-world setting, data that provide patient insights on treatment outcomes and unmet clinical and humanistic need constitute critical evidence necessary for the successful market launch of novel and effective medicines.[2] However, without the successful engagement and retention of patients over the full duration of a study period, the quality and completeness of patient-generated insights and study data are at risk. Not surprising, the focus on "patients first" has become a critical component of early planning for study success.[3,4]

If we define engagement as those design features or activities that elicit the patient's interest in a study and that inspire their willingness to enroll and actively participate, then making the study relevant and meaningful to participants, including patients directly in the design process, and minimizing data collection burden, are study success factors of paramount importance. With respect to patient retention, once a patient chooses to participate, study processes and related activities must be patient-centric and serve to spark and sustain the patient's interest and motivation to complete the study as required. Retention strategies are numerous and diverse and can include the development of patient communities or discussion forums, access to disease and health and wellness resources, to fair market compensation for time spent attending study visits, and in the case of clinical trials, important access to novel treatments. Particularly in clinical trials, study visit reminders to reduce confusion and participation burden are also commonplace. The actual engagement and retention strategies and solutions employed will vary based on such factors as study type, design parameters such as duration and assessment schedule, as well as patient characteristics and disease manifestations.

For methodological reasons, patient-centric study engagement and retention solutions appropriate for clinical trials may not always be suitable for real-world studies.

In clinical trials, study protocols mandate study visits at fixed time points and pre-defined intervals to evaluate and compare drug *efficacy* across treatments. Frequently, a full suite of patient retention and support services spanning telephone or electronic visit reminders, to concierge-style transportation services and comfort kits that minimize burden and achieve complete data for all patients at all trial time points is employed. These approaches aim to ensure that a target sample size of patients attend all protocol-defined visits, and that all data are collected, to permit high quality and sufficiently powered analyses.

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Patient retention strategies and solutions in interventional studies do not impact the integrity of the trial design, nor the study results, as the trials are designed to achieve high *internal* validity under already artificial and highly controlled experimental conditions.

On the other hand, in real-world studies and registries, where drug *effectiveness* is the focus of investigation, it is paramount, methodologically, to avoid protocol-mandated study visits and patient retention strategies that could potentially alter real-world physician and patient behaviors. If, for example, the aim of the study is to better understand patterns of usual care and drug effectiveness and tolerability, then non-persistence to treatment, and missed medical appointments are, by nature, key outcomes of interest. In this scenario, the provision of multiple reminders and transportation to the study site to enhance patient engagement and data quality may actually result in improved treatment adherence – not as a function of the treatment itself, but rather as a result of aspects of the study protocol or related procedures. While minimizing patient burden is a hallmark of a patient-centric study, care must be taken in real-world studies to minimize the extent to which the engagement and retention of patients alters naturalistic behaviors and negatively impacts the external validity, or generalizability, of the results.

If solutions are NOT tailored to the observational study paradigm, then the integrity of the study data and results can be significantly compromised and applications for the use of these real-world data will be limited.

Differences between clinical trials and observational studies that have implications for the development and application of patient identification, retention, and engagement strategies are summarized in Table 1.

As a result of these fundamental methodological differences, non-interventional prospective studies and registries require engagement and retention solutions that can be markedly different than those applicable to interventional clinical trials. Key considerations for the development of real-world strategies and solutions are presented in Table 2.

Despite some inherent challenges, there are numerous important and effective over-arching strategies for engagement and retention of patients in real-world studies that can be implemented without necessarily impacting the integrity and external validity of the observational data collected.

- Consider the involvement of patients and/or caregivers in the study design process to better understand what may inspire patients to enroll, anticipate "pain points" for participants, and to inform the development or selection of study outcomes[5]
- Partner proactively with patient advocacy groups and other resources to
  - Inform study design and objectives
  - Align study with real-world, community-based resources that can provide information and support to patients and their families
- Establish study e-forums or on-line communities for study patients to connect with each other and share experiences
  - Consider employment of patient-centric on-line data entry platforms or "hubs" that integrate data collection with patient access to health and wellness links and other "connectivity" functions

Table 1. Summary of Key Differences Between Interventional and Non-Interventional Studies that have Implications for Patient Recruitment, Retention and Engagement Strategies and Solutions.

Parameter	Characteristics	
	Clinical Trials	Observational Studies
Robust Methods: Data Validity	Achieve high ***internal*** validity; selection criteria reduce variability in patient characteristics and treatment patterns to permit empirical evaluations of treatment efficacy	Achieve high ***external*** validity; focus on representativeness of uncontrolled usual care setting and generalizability of outcomes to broad real-world patient populations
Protocol	Moderate to high complexity; typically trial protocols are medical diagnostics and procedures heavy; schedule of assessments is fixed	Low complexity; diagnostics and procedures as per usual care; schedule of assessments is typically open
Treatment Patterns and Costs	Estimate costs associated with trial treatment arms to reflect cost differences in relation to mandated treatment protocols; treatment patterns are driven by clinical trial protocol	Evaluate naturalistic patterns and associated costs of care in the usual care setting; treatment patterns are driven by real-world physician and patient decisions not the study protocol
Treatment Adherence	Under ***controlled*** conditions, need to understand reasons for non-persistence (focus on drug characteristics: tolerability, lack of efficacy, etc.); data typically used to evaluate efficacy and to identify optimal dosing regimens	Under ***uncontrolled*** conditions, need to understand reasons for non-adherence and non-persistence (focus on drug characteristics and patient behavior); data used to evaluate effectiveness and to highlight unmet need in standard of care, including factors which may result in non-persistence, missed appointments, and treatment avoidance

- Minimize study participation burden for investigators and patients through simple and streamlined study protocols and related study procedures
- Develop case report forms that are restricted to "must-have" versus "nice-to-have" study variables
- Leverage technology to collect data directly from patients separate and apart from usual care visits with consideration given to "Bring-Your-Own-Device" (BYOD) approaches

In summary, a commitment to robust methods to achieve high quality and representative data does ***not*** mean that patient-centric study engagement and retention strategies cannot be employed for real-world studies. Careful consideration, however, of the trade-offs between the natural desire to control for complete study data at regular time intervals and adherence to core principles of real-world research that aim to avoid interference with usual care is clearly warranted. ■

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Table 2. Key Considerations for Development of Patient Engagement and Retention Solutions

Focus	Key Considerations	
	Clinical Trials	Observational Studies
Investigator / Site Identification and Retention	Focus is on identification of high volume and research-savvy sites of care and clinical excellence; study budgets are substantial given need to manage investigational drug	Focus is on routine care sites in diverse settings; often research naïve; potentially harder to enroll; site contracts may take longer to execute; training materials may need to be more comprehensive but simpler in format; study budgets reflect fair market value for time and task spent on study activities
Patient Incentives to Enroll	Exposure to novel therapy (or hope of receiving if randomized to interventional arm) may drive enrollment; fair market value compensation for numerous clinical trial visits	Only fair market value compensation for usual care driven frequency of appointments permitted; patients must find meaning and relevance in the study
Patients	Track attendance for every scheduled clinical trial visit; missed assessments can be flagged and rescheduled	Track study visits as they occur; can't predict ***a priori*** at study launch when patients will attend or when they will miss visits as visit frequency is patient-specific and as per usual care
	Design and implementation of robust scheduled visit reminders; solutions and tools can be automated and technology driven	Cannot use additional reminders for usual care visits to study site as this will 1) prevent understanding of real-world patterns of care and patient and physician behaviors; 2) mask non-adherence and unmet need; and 3) impact patterns of care and inflate estimates of associated healthcare costs; reminders can be programmed for direct-to-patient questionnaires and diaries away from the study site
	Provide concierge-style transportation to study site to minimize study burden	Avoid use of aids to increase usual care visit attendance for same reasons as the need to avoid use of visit reminders
Technology	Use of patient attendance tracking tools and software to signal to the site when patient and/or physician outreach is necessary to resolve data gaps arising from missed visits	Tracking can be helpful to understand usual care visit metrics as study progresses but should refrain from using tool to alter pattern of usual care visits to study site

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