Observational (NIS) Studies in Conjunction with Utilization of Patient Support Programs

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One very important outcome of the International Council for Harmonization (ICH) meeting held in Osaka, Japan, November 5-10, 2016, was the amendment of ICH E6(R2)[1] (issued February 2017). The intent of this amendment was to encourage sponsors to implement improved oversight and management of clinical trials, and protect clinical trial data integrity while continuing to ensure the protection of human clinical trial subjects. The Assembly agreed to renew the wider package of guidelines that relate to good clinical practice (GCP) and clinical trial design, which includes updating the current guidance on interventional trials and the expansion of novel methods in support of drug registration, such as non-interventional studies (NIS), including registries and other observational study types.

The European Medicines Agency (EMA) guidance[2] increasingly requires the collection of risk-benefit data in post-authorization safety studies. Pharmaceutical companies now must take a more granular approach, examining different subpopulations to determine their respective risk-benefit balance. There is also an increasing demand from payers to conduct observational studies on a new product's effectiveness, and payers and clinicians are eager for more detailed health outcomes data to inform prescribing and reimbursement decisions.[3]

Innovative real-world study designs are also warranted in support of successful market access and reimbursement, particularly in crowded markets.

Patient Support Programs and Real-World Data Collection

Good pharmacovigilance practices (GVP) Module VI[4] defines the patient support program (PSP) as an organized system where a marketing authorization holder receives and collects information relating to the use of its medicinal products. Examples are post-authorization patient support and disease management programs, surveys of patients

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and health care providers, and information gathered on patient compliance or compensation/reimbursement schemes. Given the importance of patient wellness and the health benefits of compliance to effective treatments, PSPs are increasingly common. Through PSP frameworks, physicians receive additional information from patients and other qualified health care providers about adherence and health outcomes that can positively impact the patient through additional patient health monitoring, resulting in improved treatment compliance. Patients benefit through access to comprehensive information about their disease, disease control, and correct drug use and handling. PSPs also typically facilitate increased connectivity among patients and improved communication between patients and their physicians.

Patient support programs[5] are a useful addition to:

1) complex therapies with many side effects;

2) therapies requiring a series of treatments and/or ongoing monitoring/regulating;

3) therapies for diseases that negatively impact quality of life; and,

4) therapies requiring a delivery device.

Patient support programs drive medication and therapy compliance via:

- Inbound call support for inquiries on products, diseases, or program enrollment
- Helping patients make or break a habit
- Outbound calls to patients to support/coach them through their treatment with relevant messages and information
- Referrals to other information sources inside and outside the biopharmaceutical company
- Safety measures that mitigate risk with proper identification and reporting of adverse events to Drug Safety Structures
- Comfort and support that builds engagement

Given the enormity and cost of PSPs, real-world studies of PSP effectiveness to demonstrate their value are also occurring more frequently.[6] Randomized trials have demonstrated the effectiveness of tailored education and support compared with a "one size fits all" approach to help patients modify a range of health-related behaviors.[7] As well, numerous non-comparative, real-world studies of outcomes associated with PSPs plus treatment have also been published.[8]

Case Study: Observational Study of Treatment Outcomes in a Patient Support Program[9]

Study design: Non-interventional, longitudinal, and non-confirmatory study to explore rheumatoid arthritis (RA) treatment effectiveness and patient satisfaction.

The main objectives of the study were to:

1) examine the effectiveness of RA treatment with respect to PSPs by means of the Health Assessment Questionnaire Disability Index (HAQ-DI), Disease Activity Score (DAS28) results, and European League Against Rheumatism (EULAR) response criteria; and,

2) evaluate the contribution of PSP to disease control, treatment continuation over time, participant's satisfaction, and PSP utilization.

The primary endpoint was to determine the percentage of participants (18-99 years of age) achieving a minimal clinically important difference (MCID) in HAQ-DI at week 78.

Additional secondary endpoints included changes in:

- Disease Activity Score (DAS28) results
- Simplified Disease Activity Index (SDAI)
- Clinical Disease Activity Index (CDAI)
- Disease response criteria

Other assessments included:

- Work Productivity and Activity Impairment (WPAI)
- Compliance Questionnaire
- Treatment Satisfaction Questionnaire for Medication (TSQM) scores (effectiveness, adverse reactions, convenience, and global satisfaction)

The participant satisfaction over time in context with utilization of a patient support program (PSP) was measured by:

- Patient Activation Measure (PAM-13) – assessment of the participant's knowledge, skill, and confidence for self-management of his/her health
- Beliefs about Medicines Questionnaire (BMQ) – beliefs about medication and the necessity of medications prescribed with sub-scales of necessity and concerns. Higher scores on the necessity sub-scale represent the stronger perceptions of the participant for the necessity of their medication. Similarly, higher scores on the concerns sub-scale represent stronger concerns about the potential negative effects of their medications.
- PSP satisfaction assessment – evaluation of the participant's satisfaction with specific PSP elements

Patient Support Program core elements consisted of:

- Call centers (in and outbound)/hotlines
- Nursing services
- Starter packs
- Provision of educational materials (print and digital) regarding disease and treatment
- Treatment guides
- Other elements of the PSP varied between countries such as refill reminders, email contacts, support groups, and newsletters

Finally, serious adverse events (SAEs), adverse events (AEs) that resulted in treatment discontinuation, and non-serious malignant events were collected for patients 30 years of age or younger.

A total of 1,025 patients were enrolled in the study and received at least one dose of the RA treatment, with 679 patients completing the study. The study results (all with p-value <0.001) regarding the primary endpoint are represented below in Table 1.

Table 1. Percent of Participants Achieving MCID among PSP and Non-PSP Users

Participants with RA Receiving RA Treatment		
	PSP Users	**PSP Non-Users**
Participants Analyzed	499	526
Participants Achieving an MCID* in the HAQ-DI at Week 78	48.1%**	37.8%**

* Defined as at least a 0.22-point improvement on the HAQ-DI compared to baseline.
** **P-value** <0.001

The percentage of participants who demonstrated improvement from baseline or who remained at Level 4 [Levels: strongly disagree (1), disagree (2), agree (3), or strongly agree (4)] from baseline on the Patient Activation Measure (PAM-13) at Week 78 is presented in Table 2.

Table 2. Percent of Participants with Improved PAM-13 Scores among PSP and Non-PSP Users

Participants with RA Receiving RA Treatment		
	PSP Users	**PSP Non-Users**
Participants Analyzed	499	526
Participants Who Demonstrated Improvement or Remained at Level 4 from Baseline at Week 78 on the PAM-13	35.7%*	28.1%*
Participants Who Started and Remained at Level 4 from Baseline to Week 78 on the PAM-13	52.4% (54 out of 103)	28.9% (24 out of 83)

***P-value**=0.01

The changes from baseline means in the Beliefs About Medicines Questionnaire (BMQ) are presented in Table 3.

Table 3. Changes in Baseline Means on the BMQ among PSP and Non-PSP Users

Participants with RA Receiving RA Treatment		
	PSP Users	PSP Non-Users
Participants Analyzed	409	362
Change from Baseline Means at Week 78 on the BMQ		
Necessity		
Participants Analyzed	409	362
Mean (SD)	-0.03 (0.743)	-0.04 (0.729)
Concern		
Participants Analyzed	409	361
Mean (SD)	-0.12 (0.902)	-0.17 (0.842)

SD=Standard Deviation

PSP Satisfaction Questionnaire Responses at Week 78 are presented in Table 4.

Table 4. PSP Satisfaction by Score

PSP in Total: Score 1	Participants with RA Receiving RA Treatment: PSP Users
Participants Analyzed	336
PSP in Total: Score 1	34.2%
PSP in Total: Score 2	
Participants Analyzed	336
PSP in Total: Score 2	35.7%
PSP in Total: Score 3	
Participants Analyzed	336
PSP in Total: Score 3	1.5%
PSP in Total: Score 4	
Participants Analyzed	336
PSP in Total: Score 4	28.6%

1=Very Good; **2**=Good; **3**=Less Satisfying; **4**=I Do Not Use the Services

Baseline characteristics were similar between cohorts. During the follow-up period, the percentage of participants achieving a minimal clinically important difference in the (HAQ-DI) at week 78 was 10.3% greater in the PSP cohort than for the non-PSP cohort. The percentage of participants who either improved or started and remained at Level 4 from baseline to week 78 on the PAM-13 was 7.6% greater in the PSP cohort than for the non-PSP cohort. Patients in the PSP cohort demonstrated better understanding of medicine necessity and safety concerns. Patient satisfaction of PSP at week 78 was 98.5% in the PSP cohort.

Univariate analyses from similar studies demonstrated that medical costs for 12 months (excluding costs for biologic treatment) were 23% lower for PSP patients than for non-PSP patients. PSP patients were also found to have 22% lower disease-related medical costs than non-PSP patients. Finally, overall costs for PSP patients were 10% lower than those for non-PSP patients.[6]

PSPs contribute significantly to successful product uptake through improved patient compliance and outcomes. Given the infrastructure set-up, including call centers, nurse outreach, and multi-modal communication, they also provide an efficient framework for the collection of real-world data that can inform a variety of research questions of importance to patients, physicians, and payers alike.

Real-world studies of PSP effectiveness offer an opportunity to optimize access to innovative medicines and improve patient outcomes. Enrollment in the PSP is associated with increased treatment adherence and persistence, reduced medical costs (all-cause and disease-related), and reduced total health care costs. These data provide support for prescribing physicians to encourage enrollment in PSPs for chronic conditions and for pharmaceutical companies to further develop and invest in multifaceted PSPs.

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