Table 1: LISTING OF THE PROBABILITIES FROM UNIVARIATE ANOVAs

Subject Characteristic	PROB
AGE CATEGORY	<0.0001
STUDY PHASE	<0.0001
DISORDER	<0.0001
DURATION	0.00007
GENDER	0.94305
COUNTRY	<0.0001
GEOGRAPHIC REGION	<0.0001

Table 2: COMPLIANCE BY REGION

REGION	MEAN	STDERR	FREQ	MEDIAN
AUSTRALIA	84.1%	2.4%	39	94.1%
EASTERN EUROPE	89.7%	1.4%	109	93.8%
GREAT BRITAIN	88.1%	2.4%	39	97.1%
NORTH AMERICA	87.0%	0.4%	1781	92.4%
SOUTH AFRICA	89.9%	3.1%	23	90.9%
SCANDANAVIA	95.0%	1.9%	60	99.0%
WESTERN EUROPE	92.0%	1.2%	146	96.0%

Table 3: ADJUSTED MEANS BY AGE CATEGORY

AGE	LS MEAN
ELDERLY	91.8%
MIDDLE	89.0%
YOUNG	80.9%

Table 4: ADJUSTED MEANS BY PAIN-RELATED DISORDER

DISORDER	LS MEAN
FIBROMYALGIA	85.4%
OSTEOARTHRITIS	89.7%
PHN	86.5%

Table 5: ADJUSTED MEANS BY GEOGRAPHIC REGION

REGION	LS MEAN
AUSTRALIA	80.9%
E. EUROPE	87.7%
G. BRITAIN	85.2%
N. AMERICA	86.7%
S. AFRICA	88.3%
SCANDINAVIA	92.1%
W. EUROPE	89.5%

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USE OF AND COMPLIANCE WITH ELECTRONIC PATIENT REPORTED OUTCOMES WITHIN CLINICAL DRUG TRIALS

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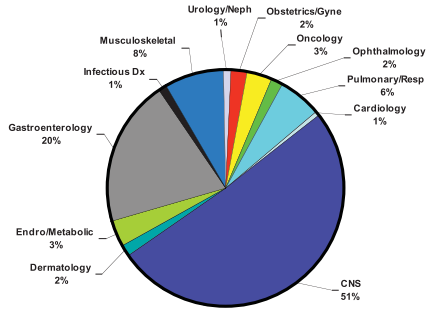
OBJECTIVES

The use of electronic patient reported outcomes (ePRO) within clinical trials has grown rapidly. This growth is due in large part to the acknowledgement by regulatory authorities that ePRO is an acceptable method to collect patient data and one that directly addresses many of the limitations of paper patient reported outcomes (PROs). To date, limited data has been published that sheds light on the types of ePRO instruments being used by clinical trials sponsors and the types of trials in which they are being implemented. In addition, there have been few published analyses of ePRO compliance across a series of studies. Where studies have been published, they have been analyses of the aggregate study characteristics (e.g. Morren 2008 European Journal of Pain) as opposed to analyses of the pooled patient individual data. This research was conducted to better understand the types of instruments being used electronically within randomized controlled trials and to investigate the compliance differences by target population demographics (e.g. age, gender, geography, etc.) within a subset of pain studies.

Graphic 1: ePRO Studies by Therapeutic Area



METHODS

A study of the characteristics of ePRO use in clinical drug trials was undertaken to understand the breath of therapeutic areas where ePRO is being used as well as to understand the dimensions affecting compliance with electronic patient reported data. A dataset of 175 clinical trials was analyzed by using fields that categorize each protocol's key elements including ePRO instrument name, trial phase, therapeutic area, disorder and mean and median compliance for patient self-reported data.

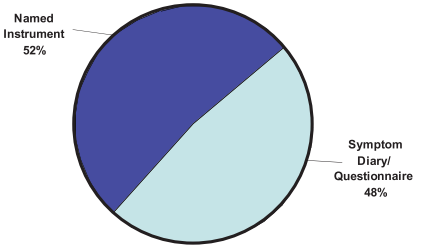
In addition, a subset of 10 pain-related studies was analyzed to understand overall compliance as well as compliance differences by indication, frequency of assessment, duration of the study, age, sex, and geographic region.

Initial exploratory analyses of the 10 studies were conducted by univariate Analysis of Variance (ANOVA) for each of the potential explanatory variables listed above. Data are presented as raw means but there was some degree of non-normality evident in the data as would be expected on a scale of 0-100. The arc-sine transformation [Snedecor GW, Cochran WG. Statistical Methods (8th ed.). Oxford: Blackwell Publishing, 1989;289-290] is commonly used with data measured on this scale and was found to be appropriate here. Thus p-values presented are from the analysis of the arc-sine transformed data. The p-values are for the overall effects from the ANOVA; pairwise comparisons between the individual groups comprising each explanatory variable were not performed.

For the raw data, both means and medians are presented. The relatively large differences between the figures are explained by the non-normal distributions including a small number of patients with zero (n=2) or low values for percentage compliance. The low compliers generally represent patients who effectively withdrew from the study at an early stage but their withdrawal was not actually registered with the IVR system until their next appointment with the investigator (in some cases the investigator withdrew the patient from the trial but also delayed the registration with the IVR system; thus, further compounding the impression of low compliance); early withdrawal is a general feature of clinical trials. Thus, to get an accurate impression of compliance it is also appropriate to consider the median.

Gender was not collected in all studies and was therefore not present for about 50% of patients. Further, there was some confounding between the explanatory variables (e.g. indication and source study) and so a multivariate analysis with simultaneous consideration of the explanatory variables is appropriate.

Graphic 2: ePRO Studies by Instrument Type

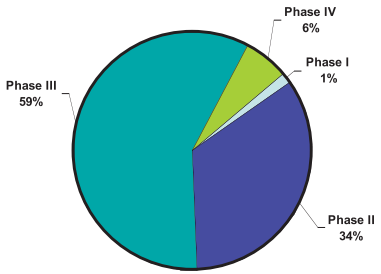


RESULTS

Breadth and depth of ePRO Use: The analysis determined that, for this dataset, CNS (89 studies) and Gastroenterology (35) studies represented almost 71% of all ePRO use by the biopharmaceutical industry (Graphic 1). Within CNS protocols, ePRO was used most frequently in depression (33%), anxiety (12.4%) and insomnia (9.1%). Outside of CNS, Opiod-induced Bowel Dysfunction (OBD) represented the largest (6.9%) use of ePRO. Overall, ePRO was used in 12 different therapeutic areas for 56 different disorders. 52% of the time a named PRO instrument is administered electronically (Graphic 2); the balance of the instruments is diaries or symptom questionnaires which may not have undergone formal validation (48%).

For this dataset, ePRO was predominately used in Phase II and III studies; combined these represented 93% of the use of ePRO (Graphic 3). ePRO was typically used in studies where the target population included both adult and elderly (50+) study subjects (Graphic 4).

Graphic 3: ePRO Studies by Study Phase



ePRO was used to collect primary efficacy data alone or in combination with other data (e.g. secondary, safety, etc.) in just over half of the studies (53%). It is interesting to note that 6% of the time, ePRO was used to collect eligibility data such as inclusion/exclusion criteria, disease severity or protocol compliance data (Graphic 5).

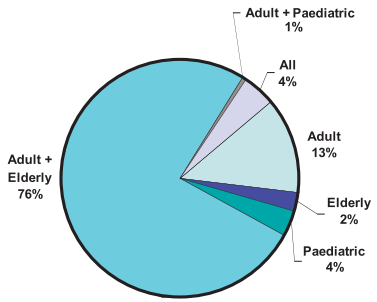
Daily assessment was the most common assessment frequency (43%), but frequencies also included weekly (7%), monthly (3%) or some combination of daily and weekly assessment (6%). Study subjects' ability and willingness to provide this data multiple times a day is demonstrated by the 8% of the studies that collected patient data twice daily (Graphic 6).

Compliance analysis: To understand the impact of patient characteristics on ePRO compliance, a sub analysis of 10 pain-related studies was performed. The indications being pursued for these studies included: fibromyalgia, osteoarthritis and post herpetic neuralgia (PHN).

Perhaps not surprisingly because of the size of the dataset all explanatory variables apart from gender were significant (Table 1). As this is an exploratory analysis, multiple comparisons between the levels of each factor were not examined. But, it was noted that compliance for elderly (≥65) patients was greater than middle-aged patients (41-64) which, in turn, exceeded younger (≤40) patients with respective means of 90.9%, 87.5% and 78.8%; the corresponding values for the median are 95.5%, 92.3% and 83.2.

Individual study mean compliance ranged from low of 81.7% compliance to a high of 93.7% while the corresponding median compliance covered a range from 88.6% to 100%. It is the belief of the authors that the median is a more accurate measure of compliance because the mean compliance is often understated by patient withdrawal and patients lost to follow up. If these study subjects are not marked as withdrawn in a timely manner, overall mean compliance will be adversely affected.

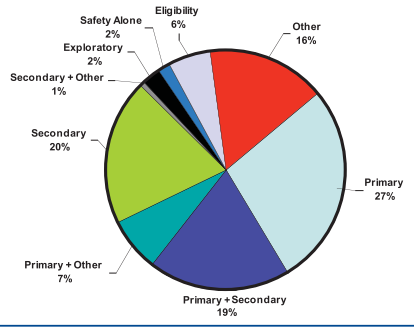
Graphic 4: ePRO Studies by Target Population



Osteoarthritis patients were the most compliant (91.7% mean; 95.2% median) study subjects versus post herpetic neuralgia subjects (89.9%; 95.2%) and fibromyalgia subjects (85.4%; 90.9%). Compliance by gender was comparable with medians compliance than 1% apart (92.9% for males vs. 91.9% for females). As gender was not significant in the multivariate analyses, the significant value is considered an artifact.

The analysis of compliance by region (Table 2) shows study subjects in Scandinavian countries to be the most compliant (Mean = 95.0%), but the small n for this subgroup means the results should be interpreted with caution. In all cases median compliance was greater than 90%.

Graphic 5: ePRO Studies by Data Type



Multivariate analyses: In the reduced dataset, the factor for Gender was not significant after correcting for the other factors and was thus not considered further. Duration of study was not significant after correcting for study, but the terms for age, disease and region were. As a further check, the model was run without study as an explanatory factor and, again, duration of study was not significant. As variation between studies is attributable to the observed and potentially other unobserved explanatory factors, the final model is presented without adjustment for study. Thus the final model comprised age, disease and region; for explanatory purposes age was fitted in two different models – one as a continuously scaled variable and one as a categorized variable.

Tables 3, 4 and 5 show the adjusted means for age category, type of pain-related disorder and geographic region from the model where age was fitted as a discrete factor.

In the model where age was fitted as a continuous variable, the coefficient for age was 0.26% i.e. compliance rises by a quarter of a percentage point with each increase of a years age. This accords with the study level analysis of Morren et al who looked at momentary pain assessment using handheld diaries; the value of their age coefficient was 0.35%.

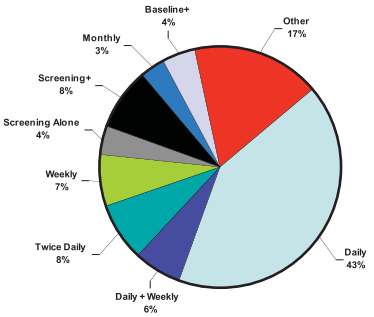
CONCLUSION

The analysis of the data set shows that electronic patient reported outcomes (ePRO) use has expanded beyond the collection of primary and secondary efficacy data to include safety, inclusion/exclusion data, and protocol/medication compliance data. Sponsors are now using ePRO for all major therapeutic areas and in all phases of clinical trials. According to this data set, more than 145 unique instruments have been administered electronically.

Compliance among patients suffering from pain-related disorders was very high for two of the key patient characteristics analyzed. Significant predictors were age, disorder and region. For age, compliance rises by a quarter of a percentage point with each increase of a years age. The differing compliance by region is interesting but is complicated by the small numbers in some of the regions and the consequent grouping over countries; further study is warranted here. While mean compliance is a useful reference, it will be understated; thus, median compliance may be a more reliable indicator of true compliance due to patients lost to follow and/or those who are not registered as withdrawn in a timely manner.

Limitations of this study include the clinical trials of this dataset which cannot be necessarily generalized as representative of all ePRO use. In addition, gender was not collected in all studies and was therefore not present for about 50% of patients.

Graphic 6: ePRO Studies by Assessment Frequency



This research shows that ePRO use within clinical trials is both broad and deep; that patients can be highly compliant; and that elderly patients are slightly more compliant when reporting their data electronically.

Mean vs. Median Compliance