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High Engagement of Patients Monitored by a Digital Health Ecosystem Indicates Significant Improvements of Key r-hGH Treatment Metrics

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Abstract. The early adoption of digital health solutions in the treatment of growth disorders has enabled the collection and analysis of more than 10 years of real-world data using the easypod™ connect platform. Using this rich dataset, we were able to study the impact of engagement on three key treatment-related outcomes: adherence, persistence of use, and growth. In total, data for 17,906 patients were available. The three features, regularity of injection (≤2h vs >2h), change of comfort setting (yes/no), and opting-in to receive injection reminders (yes/no), were used as a proxy for engagement. Patients were assigned to the low-engagement group (n=1,752) when all of their features had the low-engagement flag (>2h, no, no) and to the high-engagement group (n=1,081) when all of their features had the high-engagement flag (≤2h, yes, yes). The low-engagement group was down-sampled to 1,081 patients (subsample of n=37 for growth) using the iterative proportional fitting algorithm. Statistical tests were used to study the impact of engagement to the outcomes. The results show that all three outcomes were significantly improved by a factor varying from 1.8 up to 2.2 when the engagement level was high. These results should encourage the promotion of engagement and associated behaviors by both patients and healthcare professionals.

Keywords. Digital health, real-world evidence, engagement impact on treatment

1. Introduction

Digital health solutions are on the rise in the treatment of all kinds of conditions [1-4]. In the context of recombinant human growth hormone (r-hGH) treatment, easypod™ connect is an ecosystem comprised of a customizable electronic autoinjector device with data transmitter and a connected web interface that is accessible at any time by the

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responsible healthcare professional (HCP) [5]. This enables the collection of real-world data on patients and their injection behavior and, hence, the accurate estimation of key treatment-related parameters. While several studies have shown the impact of clinical features on key r-hGH treatment success metrics [6, 7], to our knowledge, none has investigated whether engagement with the treatment *per se* has a positive impact.

The aim of this study was to assess whether a higher engagement was associated with improved adherence, persistence of use, and growth when compared with a lower engagement level using data from the digital health ecosystem.

2. Methods

2.1. Data and feature engineering

This study focused on data from 17,906 children registered worldwide in the easypod™ connect ecosystem and having transmitted data with the easypod™ autoinjector. Readily available features of the system are pseudonymized patient information (gender, year of birth, and country), injection information (time, dose), and comfort settings (speed, depth, and duration of injection). We focused on potential explanatory variables which could be monitored through a digital health ecosystem and derived as a proxy for engagement level. Three such engagement-relevant features were developed:

1. Regularity of injection with the autoinjector, computed for each patient as the standard deviation (SD) of their recorded injection hours over the total duration of use. It is expected that, for these chronic conditions, the creation of habits and, therefore, regular injections are critical, and is a sign of strong engagement of patients/caregivers to the treatment.
2. Whether the comfort settings were left at their default value (all) or changed to a custom setting (at least one). These settings are typically changed early on when starting with the autoinjector, in consultation with HCPs. As each patient is different, a different value on at least one of the settings is likely to feel more comfortable. Changes vs default values are considered a sign of using the system's options and of strong engagement.
3. Whether or not a patient opted-in for receiving an injection reminder from the easypod™ connect ecosystem. This option, disabled by default, indicates that patients/caregivers are interested in getting support throughout the treatment to stay on track and is a sign of strong engagement.

Based on the above, the dependent variables and key treatment success metrics were:

1. Mean dose adherence over the duration of use (injected vs prescribed in %) categorized into optimal (≥85%) or suboptimal (<85%) [7] (this is a reference threshold for adherence and corresponds to approximately one missed injection/week [8]);
2. Persistence of use, defined as the time in years between the first injections and the last recorded injection in the system; patients were considered to have stopped the use if they had no injection recorded for 6 consecutive months; and
3. Cumulative gain in height SD score (ΔHSDS) normalized per number of years between the last and first measurement recorded in the ecosystem and computed based on WHO child growth charts [9], for patients with at least two recorded growth measurements.

2.2. Engagement level definitions

For every patient, each of the above engagement-relevant features was assigned a low- or high-engagement flag, as shown in **Table 1**. The median value of the injection hour SD across all population was 2 hours; this threshold was used to assign the relevant flag to the injection regularity feature.

Table 1. Engagement-relevant features and their respective low-/high-engagement assignment conditions

Engagement level flag	Engagement-relevant features		
	Comfort settings	Opted-in reminders	Injection regularity (SD)
Low	Default	No	>2h
High	Custom	Yes	≤2h

Finally, patients were assigned to the low-engagement group when **all** of their features had the low-engagement flag, to the high-engagement group when **all** of their features had the high-engagement flag, and were discarded in the case of mixed flags (as these did not allow us to clearly assess engagement).

2.3. Data sampling and statistical methods

Filtering the data as per the above-described methodology led to an imbalance in the size of low- and high-engagement groups (1,752 and 1,081 patients, respectively). To remove this size imbalance and the potential bias introduced by the gender and age distribution mismatch between the two groups, the low-engagement group was down-sampled to 1,081 patients using the iterative proportional fitting (IPF) algorithm along the age and gender dimensions [10, 11]. The number of patients was now 1,081 in each group, with 59% male in the low- and 58% in the high-engagement group, and the median age at start of use was 10 years in each group. While adherence to treatment and persistence of use could be calculated for all patients, comparing the ΔHSDS achieved at end of use was conditioned by having stopped use and having had at least two height measurements recorded in the system during use. This was the case for only 37 patients in the high-engagement group and 86 patients in the original low-engagement group. The numbers are low because growth data is not recorded automatically – it has to be entered manually by the HCP involved and so are not routinely available for all patients. The same IPF under-sampling procedure described above was repeated on the reduced dataset with available ΔHSDS information, leading to 37 patients in each group: gender male was 67% and 70%, and median age at start of use was 10 and 11 years, in the low- and high-engagement groups. The two groups were compared in terms of percentage of patients with suboptimal adherence, median persistence of use and ΔHSDS distribution (median 25th and 75th percentiles). To estimate the median persistence of use and the probability of continuing the use of the digital ecosystem over time, the Kaplan-Meier model [12] was employed. The statistical significance tests utilized to compare groups were: Wilcoxon rank sum for ΔHSDS, chi-squared for the proportion of suboptimal adherent patients, and log-rank for the persistence of use. The relative impact of the three engagement-relevant features on each of the different treatment success metrics was evaluated with the permutation feature importance technique [13] in conjunction with a Random Forests [14] prediction model (10 runs): randomly shuffling the values of each feature and evaluating the subsequently generated loss in prediction accuracy enabled hierarchizing them by importance.

3. Results

Compared with patients in the low-engagement group, those highly engaged both to their treatment and with the easypod™ connect digital ecosystem showed significantly better treatment characteristics in all three metrics of interest (**Table 2**). Suboptimal adherence rate decreased by a factor of 1.8 ($p<0.001$) and the estimated median persistence of use increased by a factor of 1.9, from 1.8 years to 3.2 years ($p<0.001$), in the case of highly-engaged patients (n=1,081) compared with low-engaged patients (n=1,081). The highly-engaged patients in the reduced ΔHSDS dataset of 37 patients per group had a median ΔHSDS per year more than double vs the low-engagement group (0.68 vs 0.31, $p=0.02$).

Table 2. Comparative results between low- and high-engagement groups

Treatment characteristic	Low-engagement group	High-engagement group	p-value
Patients with suboptimal mean adherence	31%	17%	<0.001
Median estimated persistence of use, years	1.8	3.2	<0.001
Median ΔHSDS per year	0.31	0.68	0.02

For all three key treatment metrics, the regularity of the injection time had the greatest impact, followed by customized settings and opting-in for reminders. The relative permutation feature importance of adherence showed median values of 1.17 for regularity of injection time, 0.44 for the use of custom settings, and 0.16 for the use of reminders (numbers in arbitrary units). This was similarly observed for persistence of use and growth.

4. Discussion

Our study relied on accurate adherence and injection data and provides real-world evidence for the positive impact of high engagement as part of the treatment with r-hGH. The results should encourage the promotion of engagement and associated behaviors (e.g. finding optimal comfort settings or recommending regular injections) to patients in the low-engagement group and, where applicable, to those who showed mixed-engagement flags and were discarded from the comparison study.

Moreover, the presented methodology could be replicated to various medical conditions benefiting from a digital health solution, provided that accurate, reliable data are available from the solution used. Data availability is indeed a frequent obstacle to conducting such analyses, including ours. For instance, more features could be relevant for engagement, but many of the available system options are rarely used in practice, or are simply missing, such as recording medical visits or tracing connections to the web interface. It would benefit researchers if more clinicians would add the individual patient's growth data to the data collected automatically by the easypod™ device.

5. Conclusions

We leveraged data analytics and machine learning techniques on real-world data to test whether high engagement of patients with the treatment had a positive impact on three key r-hGH treatment metrics: adherence, persistence, and growth. Our results showed statistically significant improvements in all three treatment dimensions. The methodology can be applied to data obtained from several digital health systems. We confirmed that habits of a regular treatment schedule combined with high engagement with the digital therapeutics system, such as using custom injection settings and reminders, can be beneficial for r-hGH treatment. These findings should encourage the use of solutions to empower patients to adhere to treatment schedules and the large-scale adoption of digital tools involving most prominent engagement factors, which in turn would enable HCPs to make more informed decisions towards improved treatment outcomes.

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Conflicts of interest

EK is an employee of Merck KGaA and holds shares in the company. LA and QLM are employees of Ares Trading SA, an affiliate of Merck KGaA, Darmstadt, Germany. PvD has a consultancy agreement with Merck KGaA.

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