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CLINICAL FEATURES
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Real-world changes in US health system hospital-based services following treatment with a prescription digital therapeutic for opioid use disorder

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ABSTRACT

Outcomes associated with buprenorphine therapy for the treatment of opioid use disorder (OUD) are suboptimal. reSET-O is an FDA-authorized prescription digital therapeutic (PDT) delivering neurobehavioral therapy via mobile devices to patients with OUD treated with buprenorphine. This analysis evaluated the net impact of reSET-O on medical costs among actively-engaged reSET-O patients using real-world observations. This real-world retrospective analysis of health care claims between October 2018 and October 2019 evaluated health care resource utilization up to 6 months before and 6 months after the initiation of a reSET-O prescription after accounting for the subset of patients not continuing on therapy after week 1 (non-engaged patients). Repeated-measures negative binomial models compared incidences of hospital-based encounters/procedures adjusted for days in each period as well as associated costs. The number needed to treat (NNT) to avoid an inpatient visit was calculated. Of the 351 patients who were prescribed reSET-O, 321 met the criteria of active engagement. Treatment with reSET-O was associated with a substantial reduction in medical costs of -$765,450 (-$2,385/patient, $235/patient greater than a previous analysis in which non-engaged patients were included) in the 6-month period after initiation. The gross reSET-O prescription cost of $584,415 ($1,665/patient) was substantially offset by $49,950 ($142.31/patient) in refunds to payers. The medical cost reduction in engaged patients offset the cost of the therapeutic resulting in an overall cost reduction of -$230,985 in this cohort (net savings of -$720 per patient). The number needed to treat to avoid an inpatient visit was 4.8. Engagement and continued treatment with reSET-O in patients with OUD treated with buprenorphine is associated with substantial real-world reductions in medical costs in the 6-month period following the initiation of the reSET-O prescription.

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Introduction

The economic and societal burden of opioid use disorder (OUD) has been further exacerbated by the COVID-19 pandemic [1]. Prior to the pandemic, the cost of OUD to the US healthcare system alone was already an estimated $70-90 billion annually, largely driven by excess hospital and emergency department (ED) encounters [2,3]. The COVID-19 pandemic has disrupted access to OUD treatment programs and it has increased social isolation, stress, anxiety, depression, alcohol use, rates of relapse, and fatal and non-fatal overdoses [4-6]. Indeed, data from April and May 2020 showed the largest monthly increases in opioid deaths ever recorded since provisional 12-month estimates began to be calculated in January 2015 [7].

Medications for Opioid Use Disorder (MOUD), along with behavioral therapy, are standard of care for OUD [8]. The most commonly-used MOUD is buprenorphine, which is associated with near-term reduced use of high-cost health care services such as inpatient stays, ED visits and hospital outpatient visits [9-11]. Unfortunately, only 1 in 4 outpatient treatment facilities in the US offer MOUD [12], and between 80% and 90% of adults in need of MOUD and/or behavioral therapy do not receive recommended care [13]. Common reasons for this unmet need include cost, stigma, and limited access to treatment (including behavioral therapies) [14]. The few providers authorized to provide MOUD often prescribe these medications far below their patient limits [15]. Patients in rural communities, where substance use treatment centers or addiction specialists may be non-existent or difficult to access, are particularly vulnerable and disadvantaged [12].

Prescription digital therapeutics (PDTs) are evidence-based software therapeutics that deliver on-demand treatment that is evaluated for safety and effectiveness in randomized clinical trials (RCTs), and authorized by the U.S. Food and Drug Administration (FDA) to treat disease with approved directions for use. The reSET-O PDT received FDA market authorization in late 2018 for increasing retention in treatment, and is a 12-week treatment for patients with OUD at any stage of buprenorphine treatment [16]. Prescribed by clinicians, reSET-O can safely expand use of the behavioral component of treatment by giving patients 24/7 access to therapeutic content. This may help address the issues of limited access to clinicians,

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either because of geographical variations, lack of viable appointment time slots for individual patients, or as a result of restrictions on face-to-face interactions due to the COVID-19 pandemic. Digital delivery of the behavioral content also helps ensure that the intervention is identical across all patients, increasing its fidelity and consistency across the treated population.

reSET-O's therapeutic content is derived from the *community reinforcement approach* (CRA), and delivers clinically-validated cognitive behavioral therapy (CBT) via brief lessons (or modules) that are intended to help patients avoid illicit opioids, build constructive interpersonal relationships, and establish long-term constructive behaviors and resiliency [17-21]. Following activation, reSET-O's therapeutic content is available for 12 weeks, during which time patients are encouraged to complete four lessons per week in order to maximize efficacy. Immediately following each lesson, patients take a simple quiz intended to increase comprehension and retention of the therapeutic content just covered (this is known as 'fluency training'). After completion of up to four lessons and fluency training sessions per week, patients are eligible to receive contingency management (CM) to provide immediate positive reinforcement for the lessons completed, and for the achievement of negative urine drug screens [22]. Administration of CM is handled algorithmically by the PDT, although the care team is able to log negative urine drug screens via the clinician dashboard in order to enable additional CM rewards.

In the pivotal RCT on which FDA authorization for reSET-O was based, 82% of the 170 adult patients with OUD who received treatment with the therapeutic remained in treatment, versus 68% of those who only received treatment as usual (TAU – consisting of buprenorphine, 30 minutes of face-to-face counseling every other week, and contingency management). The likelihood of abstinence during weeks 9–12 was 77.3% vs. 62.1%, respectively ($P < 0.05$ for both comparisons) [19-23]. Although RCTs are the gold standard for evaluating safety and efficacy of therapeutics, they are conducted under tightly-controlled conditions optimized to ensure maximum scientific validity. Real-world evidence complements RCTs by evaluating the generalizability of therapeutic use in the context of actual day-to-day clinical care [24,25]. A recent real-world study involving 3,144 patients treated with reSET-O, for example, found that reSET-O is readily and broadly used by patients with OUD and that high engagement with the therapeutic was positively associated with abstinence and retention in treatment [26]. A separate real-world evaluation of 351 patients treated with reSET-O demonstrated that hospital facility utilization (i.e., hospitalizations, emergency department, observation visits, partial hospitalizations) accounted for ~70% of the reduction in costs ($2,150/patient) following the initiation of reSET-O [27]. In that cohort, however, some patients discontinued the therapeutic after the first week, triggering a reimbursement to a third-party payer for those prescriptions. Therefore, the objective of this analysis was to determine the net-cost of reSET-O to third-party payers, using real-world utilization patterns. This was accomplished by conducting a pre-post analysis that evaluated changes in healthcare resource utilization and associated costs among this cohort for the 6 months prior-to and following engagement with reSET-O.

Methods

This was a real-world, retrospective pre-post cohort analysis of health care resource utilization (HCRU [Hospital facility and clinician services]) via medical claims data.

Population

The patient population has been previously described [27]. Briefly, 351 patients prescribed reSET-O between 10/01/2018 and 10/31/2019 and who successfully activated the therapeutic (thereby triggering a health insurance claim) were identified from a large medical and pharmacy database (Health Verity Private Source 20) representing over 150 Commercial, Medicaid, and Medicare Advantage Payers. Thirty individuals were removed due to failure to engage with reSET-O after 1 week, resulting in a final sample of 321 patients. All patients in this analysis were treated by their clinicians in typical care settings and were not part of a clinical trial.

Study measures

This analysis evaluated patient demographic characteristics including age, sex, payer type, and OUD diagnosis type. The index date was defined as the date of initiation of reSET-O PDT. Health care resource utilization was evaluated at the hospital facility level (DRG codes for all-cause inpatient stays [IPs], intensive care unit [ICUs] stays, ED visits, partial hospitalizations [PH], and surgical outpatient department [SOD] visits), and at the clinician services level (all CPT codes). The primary outcome was the average net-cost incurred by third-party payers on behalf of patients with OUD who were being treated with buprenorphine and reSET-O, after accounting for potential cost offsets associated with reduction in high-cost HCRU during the 6 months following engagement with reSET-O, relative to the 6 months prior to engagement.

Analyses

The following process was followed to calculate the net cost impact of reSET-O. First, the net cost of reSET-O was calculated by subtracting the reimbursement amount for patients who did not engage with the therapeutic after week 1, from the upfront cost for all reSET-O prescriptions (the cost of the reSET-O prescription includes the cost of delivering the CRA neurobehavioral content, along with fluency training, and fully automated contingency management).

Next, change in HCRU was calculated by subtracting the number of events for each utilization category in the 6 months post-index from the number of utilization events in the 6-month pre-index period, as shown in the example below:

Absolute change in IP $stays_i$ = total IP stays post-$index_i$ – total IP stays pre-$index_i$

Standardized costs were obtained from the literature (Table 1) and applied to each utilization category, after adjusting to 2020 values where necessary [28]. The pre-post absolute

Table 1. Standardized costs for hospital facility.

Service Category	Cost Input (2020-adjusted)	Source
Hospital Facility Services		
Inpatient Stay	$12,476*	Premier**[29]
ICU Stay	$21,802*	
Emergency Department Visit (treat and release)	$536*	
Partial Hospitalization	$5,100	2020 CMS Fee Schedule***[30]
Surgical Outpatient Department Visit	$1,996	
Clinical Services		
Pathology and laboratory: Drug testing	$70	2020 CMS Fee Schedule***[30]
Medicine: psychiatry	$77	
Evaluation and Management (E&M): Office/other outpatient services	$100	
Pathology and laboratory: Other	$50	
Rehabilitative services: Behavioral health	$30	
Rehabilitative services: Alcohol & substance	$75	
E&M: Case management services	$42	
Medicine: physical medicine and rehabilitation	$50	
Rehabilitative services: Mental health	$14	
Surgery	$630	
E&M: Hospital inpatient services	$200	
Medicine: cardiovascular	$104	
Transport services	$30	
E&M: Domiciliary rest home	$110	
Medicine: chiropractic manipulative treatment	$50	
Radiology	$100	
E&M: Emergency department services	$200	
Medicine: hydration therapeutic prophylactic diagnostic injections and infusions and chemotherapy and other highly complex drug or highly complex biologic agent administration	$100	
Medicine: special services procedures and reports	$100	
Drugs administered other than oral method: Other	$30	
Medicine: ophthalmology	$104	
Medicine: noninvasive vascular diagnostic studies	$166	
Medicine: pulmonary	$104	
E&M: Consultation services	$42	
Medicine: acupuncture	$30	
Anesthesia	$50	
E&M: Prolonged services	$200	

* Adjusted to 2020 US Dollars
** Represents Hospital Charge Data
*** Represents average cost across similar services

change in costs was then calculated by multiplying the absolute change in events in each category by the standardized cost for that category, as shown in the example below:

Absolute change in IP $cost_i$ = Absolute change in IP $stays_i$ ´ $12,476

Total change is the sum of all pre/post cost changes across all service categories.

The last step in the calculation of the net cost impact of reSET-O from a third-party payer perspective involved adding the reSET-O net price to the pre-post absolute change in medical costs. The cost impact per treated patient was calculated by dividing the resultant cost by the size of the cohort of patients who engaged with the therapeutic beyond week 1.

Lastly, the number needed to treat (NNT) to avoid a facility encounter was calculated using the cumulative event proportions formula which calculates the absolute risk reduction (ARR) as a function of the number of life-years of the observation period, as shown below:

$$R_0 = 1 - e^{(-\text{Baseline Events/Time})}$$
$$R_1 = 1 - e^{(-\text{follow-up Events/Time})}$$
$$ARR = R_0 - R_1$$
$$NNT = 1/ARR$$

Results

Demographics

Of the 321 patients who engaged with reSET-O and continued treatment beyond week 1, the majority (82.2%) were covered by Medicaid, and were highly adherent to buprenorphine in the 6 months prior to the initiation of reSET-O (medication possession ratio: 0.74) (Table 2).

Net economic impact of reSET-O

The calculation of the net cost of reSET-O, accounting for the amount refunded to payers for these patients, is shown in Table 3. Net prescription cost was $534,465 after $49,950 in refunds for the 30 non-engaging patients.

As shown in Table 4, the net pre/post cost change in facility services was -$622,702 (-$1,940 per patient). After accounting

Table 2. Patient demographics and characteristics.

Demographic/characteristic	N = 321
Age on index date	
Mean (SD)	36.8 (8.50)
Median	36.0
IQR	31.0–41.0
Range	20–67
Age on index date, n (%)	
18–24	13 (4.0%)
25–34	124 (38.6%)
35–44	136 (42.4%)
45–54	32 (10.0%)
55–64	14 (4.4%)
65–74	2 (0.6%)
Sex, n (%)	
Male	122 (38.0%)
Female	199 (62.0%)
Payer on index date, n (%)*	
Commercial	41 (12.8%)
Medicaid	264 (82.2%)
Medicare Advantage	8 (2.5%)
Unknown	8 (2.5%)
Buprenorphine Treatment	
Pre-Index, n (%)	256 (76.7%)
Post-Index, n (%)	243 (72.8%)
Buprenorphine adherence Pre-Index (MPR), adjusted mean (SE)	**0.74 (0.02)**
Buprenorphine adherence Post-Index (MPR), adjusted mean (SE)	**0.83 (0.02)****

IQR, interquartile range; SD, standard deviation. *Percentages may add to more than 100% as patients claims may be included for different opioid use disorder indications.
**Denotes statistically significant difference vs. the pre-index period ($P = 0.04$)

Table 3. Calculation of reSET-O net prescription cost.

reSET-O List Price	Number of Prescribed Patients	Total Prescription Cost	Non-engaging Patients	Total Refund to Payer	reSET-O Net Prescription Cost
$1,665	351	$584,415	30	$49,950	$534,465

Table 4. Change in facility and clinical service encounters relative to reSET-O initiation, and calculation of associated costs (encounter categories ranked by magnitude of change).

Service Category	Pre-Index Encounters (95% CI)	Post-Index Encounters (95% CI)	Pre-Post Change* (95% CI)	Cost Difference
Facility Services				
Inpatient Stay	62 (30, 131)	19 (11, 35)	−43 (−90, 5)	-$536,643
ICU Stay	4 (2, 11)	0 (0)	−4 (−11, −2)	-$90,980
Emergency Department Visit (treat and release)	129 (96, 173)	96 (67, 138)	−33 (−76, 11)	-$17,550
Partial Hospitalization	10 (2, 59)	16 (4, 68)	+6 (−23, 36)	+$32,742
Surgical Outpatient Department Visit	5 (2, 12)	0 (0, 3)	−5 (−12, 2)	-$10,272
Subtotal	**206 (149, 284)**	**129 (91, 182)**	**−77 (−152, −2)**	**-$622,702**
Clinician Services				
Pathology and laboratory: Drug testing	3,114 (2781, 3486)	2,477 (2181, 2813)	−637 (−912, −362)	-$44,603
Medicine: psychiatry	2,490 (2146, 2890)	2,142 (1837, 2498)	−348 (−671, −25)	-$26,773
E&M: Office/other outpatient services	3,878 (3492, 4305)	3,672 (3332, 4048)	−205 (−491, 79)	-$20,544
Pathology and laboratory: Other	1,141 (940, 1385)	959 (774, 1188)	−182 (−332, −32)	-$9,100
Rehabilitative services: Behavioral health	179 (99, 326)	274 (140, 535)	+95 (−252, 62)	+$2,841
Rehabilitative services: Alcohol & substance	417 (246, 706)	332 (168, 656)	−85 (−276, 106)	-$6,356
E&M: Case management services	2,063 (1423, 2991)	2,141 (1472, 3115)	+78 (−704, 549)	+$3,263
Medicine: physical medicine and rehabilitation	141 (67, 295)	211 (88, 502)	+70 (−245, 105)	+$3,499
Rehabilitative services: Mental health	84 (58, 101)	145 (73, 289)	+62 (−153, 30)	+868
Surgery	263 (218, 318)	201 (158, 257)	−62 (−123, 0)	-$38,836
E&M: Hospital inpatient services	48 (25, 94)	97 (47, 199)	+49 (−124, 27)	+$9,694
Medicine: cardiovascular	103 (70, 152)	56 (36, 87)	−47 (−82, 11)	-$4,888
Transport services	72 (40, 154)	108 (42, 274)	+36 (−128, 55)	+$1,079
E&M: Domiciliary rest home	105 (69, 159)	139 (93, 221)	+34 (−75, 7)	+$3,778
Medicine: chiropractic manipulative treatment	43 (12, 147)	76 (23, 258)	+34 (−140, 73)	+$1,685
Radiology	193 (157, 237)	161 (123, 212)	−31 (−79, 17)	-$3,114
E&M: Emergency department services	147 (110, 196)	117 (83. 165)	−30 (−81, 21)	-$5,971
Medicine: hydration therapeutic prophylactic diagnostic injections and infusions and chemotherapy and other highly complex drug or highly complex biologic agent administration	103 (77, 137)	73 (48, 111)	−30 (−67, 6)	-$3,017
Medicine: special services procedures and reports	52 (27, 101)	34 (17, 69)	−18 (−47, 11)	-$1,798
Drugs administered other than oral method: Other	119 (90, 157)	133 (57, 310)	+14 (−130, 101)	+$433
Medicine: ophthalmology	28 (18, 41)	18 (10, 33)	−10 (−26, 6)	-$1,035
Medicine: noninvasive vascular diagnostic studies	17 (9, 32)	8 (3, 20)	−9 (−21, 2)	-$1,547
Medicine: pulmonary	33 (21, 52)	24 (13, 45)	−9 (−27, 9)	-$968
E&M: Consultation services	12 (7, 22)	19 (9, 41)	+7 (−9, 22)	+$270
Medicine: acupuncture	12 (2, 63)	6 (1, 46)	−6 (−29, 18)	-$183
Anesthesia	20 (12, 34)	15 (8, 31)	−5 (−20, 10)	-$241
E&M: Prolonged services	57 (31, 107)	53 (27, 103)	−4 (−20, 11)	-$899
Subtotal	**14,898 (14431, 16,522)**	**13,604 (12240, 15122)**	**−1,291 (−2475, −108)**	**-$152,403**
Total	**15,103 (13617, 16,750)**	**13,729 (12355, 15257)**	**−1,372 (−2580, −165)**	**-$765,450**

*Negative and positive signs indicate a reduction or increase, respectively, in utilization post-index vs. pre-index.

for additional changes in clinician services (-$152,450) the net pre/post cost change in medical costs was -$765,450 or -$2,385 per patient (Table 5).

When the net reSET-O prescription cost (Table 3: $534,465, or $1,665 per engaged patient] is added to the net change in medical costs (Table 4: -$765,450, or -$2,385 per engaged patient), the result is a savings of -$230,985 ($720 per engaged patient).

Table 5. Summary of hospital-based utilization cost changes.

	Number of Episodes	Projected Cost of Episodes	Cost Difference Per Patient
Utilization Reduced			
Facility Services	−85	-$655,444	-$2,042
Clinician Services	−1726	-$170,157	-$530
Subtotal	−1811	-$825,601	-$2,572
Utilization Increased			
Facility Services	55	$42,436	$132
Clinician Services	477	$17,715	$55
Subtotal	532	$60,151	$187
Net Impact	−1279	-$765,450	-$2,385

NNT calculation

The ARR for any hospital facility encounter was 21% (62 events in the pre-index period ($R_0 = 1 - e^{(-62/160\ [5].\ \text{patient years})} = 0.32$) vs 19 events in the post-index period ($R_1 = 1 - e^{(-\ [18]/160\ [5].\ \text{patient years})} = 0.11$)), resulting in an NNT of 4.8 (1/ARR = 1/0.21).

Discussion

This real-world analysis of changes in HCRU and associated costs among 321 patients with OUD who were treated with buprenorphine and reSET-O, revealed a mean savings/net-benefit of $720 per-patient to third-party payers in the 6 months following initial engagement with the digital therapeutic, compared to the 6 months prior. This is $235 per-patient more than our prior analysis, which revealed a savings/net-benefit of $485 per-patient over the same time-frame, but also included individuals who did not engage with reSET-O after the first week [27]. A quick calculation reveals that the additional cost associated with those who did not engage

with reSET-O was substantial. In this analysis, costs were reduced by $765,264 ($2,384/patient x 321 patients), versus a reduction of $754,650 ($2,150/patient x 351 patients) in our prior analysis, indicating that non-engaged patients utilized an additional $353.80 worth of healthcare resources, on average ($765,264 – $754,650 = $10,614; $10,614 ÷ 30 patients = $353.80/patient), during the same time period.

Cost reductions were driven by a marked decrease in hospital-based services use (79 fewer) in the 6-months following reSET-O initiation compared to the preceding 6 months and overall by the 1,326 fewer encounters across facility and clinician services. Notably, there was a substantial reduction in the number of IP stays (62 vs. 19) and all hospital-related visits post index (210 vs. 131) observed in this analysis. This decrease in hospital-related visits (43 per 321 treated patients over 6 months, equivalent to a number-needed-to-treat of 4.8) represented 70% of the cost reduction observed following reSET-O exposure. Considering the high rates of buprenorphine treatment and adherence during the 6 months prior to engagement with reSET-O, these results suggest a substantial additional benefit of reSET-O to buprenorphine therapy in real-world, usual care conditions.

The cost savings and reductions in HCRU reported here are highly relevant given reported increases in the past decade in opioid-associated overdose admissions to intensive care units [31], and the general increase in ED visits for substance use disorders [32]. Patients with OUD receiving incremental levels of treatment are in a better position to avoid exposure to licit and illicit opioids, greatly reducing their risk of an overdose or acute care event [33,34]. The findings of this analysis are also consistent with other published claims data analyses in patients with OUD. Studies by Lynch et al., and Ruetsch et al., have shown decreased ED and inpatient visits among patients with OUD who received more comprehensive therapy [34], and among patients with increased adherence to OUD pharmacotherapy, respectively [11]. The observation that patients who did not engage with the therapeutic were more expensive, on average, is also consistent with the findings from these studies. The present analysis also observed increases in encounters that may indicate greater patient engagement with treatment, such as mental and behavioral rehabilitative services (which increased by 74% and 53%, respectively) [11,34,35].

This patient cohort reflects current treatment selection dynamics for reSET-O on behalf of both patients and clinicians, as evidenced by the relative high adherence to buprenorphine therapy, and higher proportion of female patients compared to national-level OUD statistics, and may not translate to other patient groups. Similarly, most patients in this analysis were covered by Medicaid, hence the results may not generalize to patients with other types of insurance, or without insurance. Medicaid patients often have more comorbidities and face greater socioeconomic challenges than non-Medicaid-insured patients [36,37], which may translate into different results for non-Medicaid populations. Nevertheless, the database used in this analysis has broad representation across payer types, which supports the generalizability of the results to current patients with OUD in the U.S, although the impact on uninsured patients will need further evaluation. Another limitation is the lack of reliable data regarding location of service and associated cost in this particular dataset, which required the analysis of facility and clinician services utilization tied to standardized costs rather than the more traditional approach of partitioning services and costs across inpatient, outpatient, emergency department and pharmacy utilization. However, this did not affect the measurement of total utilization of health services by patients with OUD, many of which would be associated with hospital encounters. Lastly, as with any observational research approach, causality cannot be inferred or established from this analysis. Although the early associations between exposure to reSET-O treatment (or lack thereof) and frequency of hospital stays are encouraging, future analyses with larger sample sizes that control for confounding are warranted to better measure the real-world impact of reSET-O.

The pre/post study design may introduce some bias because patients in the pre-index period (i.e., before intensification of OUD treatment with reSET-O) may have higher levels of health care resource utilization compared to the post-index period. However, it was observed that patients were experienced with buprenorphine treatment and had high levels of adherence prior to initiating reSET-O, which increases confidence in the value of providing neurobehavioral treatment in addition to buprenorphine treatment. Furthermore, this approach of having each patient act as his or her own control avoids the potential bias involved with comparing to potentially dissimilar populations which may be at a different readiness for change state [38].

Lastly, the lack of data beyond 6 months of reSET-O engagement is a limitation, which was driven by the relatively low number of patients with more than 6 months of follow up at the time of this analysis. Future analyses are planned to assess longer-term outcomes, relative to matched controls.

Conclusions

In a cohort of patients with OUD being treated with buprenorphine who engaged with the reSET-O PDT, delivering OUD-specific cognitive behavioral therapy, fluency training, and contingency management, HCRU were substantially reduced. The findings from this analysis of a real-world population suggest potential for near-term (< 6-month) savings for third-party payers. The number-needed-to-treat to avoid one inpatient stay was low, with one inpatient stay avoided for every five patients treated with reSET-O. This analysis suggests that PDTs may have value in helping to overcome geographic and logistical barriers to the delivery of appropriate and timely supportive neurobehavioral therapy.

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FFV: Employee of Pear Therapeutics, Inc.
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