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The Impact of COVID-19 Regulations on Adherence to Recombinant Human Growth Hormone Therapy: Evidence from Real-World Data

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Abstract: Worldwide regulations during COVID-19 positively and negatively impacted self-management in paediatric patients with chronic medical conditions. We investigated the impact of regulations on adherence to recombinant human growth hormone (r-hGH) therapy in paediatric patients with growth disorders, using real-world adherence data extracted March 2019–February 2020 (before COVID-19) and March 2020–February 2021 (during COVID-19) from the easypod™ connect ecosystem. Data from three measures of regulations were analysed: stringency index (SI), school closure and stay-at-home. The mean SI, and the proportion of days with required school closure or stay-at-home during COVID-19 were categorised as high versus medium/low based on the 75th percentile. Adherence was categorised as optimal (≥85%) versus suboptimal (<85%). Adherence data were available for 8915 patients before and 7606 patients during COVID-19. A high SI (mean ≥68) and a high proportion of required school closure (≥88%) resulted in an increase in the proportion of optimal adherence during COVID-19 versus pre-COVID-19 ($p < 0.001$). Stay-at-home requirements showed no statistically significant effect ($p = 0.13$). Stringent COVID-19 regulations resulted in improved adherence to r-hGH therapy in patients with growth disorders, supported by connected digital health technologies. Insights into patient behavior during this time are useful to understand potential influences and strategies to improve long-term adherence to r-hGH.

Keywords: adherence; COVID-19; growth disorders; injection device; lockdown; recombinant human growth hormone (r-hGH)

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1. Introduction

The World Health Organization declared the COVID-19 outbreak as a global pandemic on 11 March 2020 and, in response, countries implemented several regulations to limit the number of infections. As a result, COVID-19 caused profound worldwide disruption to everyday social and economic life [1]. To understand which policies could be effective in controlling the pandemic, data has been collected on the timing and stringency of regulations around the world [2]. These collected data are also freely available for research, providing an opportunity to understand the impact of COVID-19 regulations on various outcomes. One important outcome is the health of people, including the health of patients with both chronic and acute medical conditions, as global shortages of medicines and inadequate or inaccessibility to healthcare services rose during the pandemic, with low- or middle-income countries most affected; this comprises patient care and treatment adherence as well as exerting strain on healthcare professionals (HCPs) [3–5].

Poor and inconsistent adherence to treatment compromises patient outcomes [6,7]; this is well-documented in children with growth hormone deficiency (GHD) where suboptimal growth is associated with poor adherence to recombinant human growth hormone (r-hGH) therapy [8]. However, the COVID-19 pandemic has seemingly positively impacted treatment adherence and self-management in paediatric patients with chronic medical conditions. A recent study conducted in Italy reported that adherence to r-hGH increased during the COVID-19 pandemic in both paediatric and adult patients [9], possibly due to restrictions on being away from home, which has previously been reported as a barrier to adherence [10]. In children, especially, restriction of outdoor activities, with more time at home under parental supervision may increase treatment adherence. However, during the aforementioned study, medication shortage and inaccessibility to pharmacies were recognised as contributing factors for missed injections, yet these challenges were resolved by the hospital's Endocrinology Unit [9].

Ongoing monitoring and promotion of adherence and self-management is important in patients with chronic conditions [11]. The use of remote monitoring technologies such as telemedicine or virtual care to evaluate and manage patients became invaluable during the pandemic [12], and electronic monitoring to assess medication adherence has been widely studied for several years [13]. In the context of growth disorders, one such electronic monitoring device is the easypod™ electromechanical injection device (Merck Healthcare, KGaA, Darmstadt, Germany), in combination with easypod™ connect, a web-based adherence decision support system (ADSS), which reliably records the date, time, and dose administered for patients receiving r-hGH (somatropin (Saizen®); Merck Healthcare KGaA, Darmstadt, Germany) [14]. Patients can wirelessly transmit recorded data to the easypod™ connect ecosystem enabling HCPs to monitor individual patients' adherence to r-hGH based on data retrieved from their easypod™ device [14]. The use of this connected injection device to improve adherence among paediatric patients with growth disorders receiving r-hGH has been demonstrated in observational studies [15,16].

There is growing interest in the use of patient-generated data for public health, and this includes the use of connected devices [17]. Additionally, mobile technologies have been used to track issues related to the COVID-19 pandemic [18]. In this current research, we explore the use of 'big data' captured from connected injection devices to study changes in adherence behaviours during COVID-19. This is a novel approach to study, on a large scale, the use of real-world data to better understand changes in self-management behaviours during a major public health crisis.

In this present analysis, global data obtained from easypod™ connect were used to investigate the impact of COVID-19 regulations on adherence to r-hGH therapy in patients with growth disorders, using connected digital health technologies to provide a public health real-world insight into adherence behaviours from which lessons can be learned for the future. Furthermore, investigating the feasibility of digital health is important to better understand adherence behaviour in relation to the variable social construction of childhood [19]. It may also prove particularly beneficial when face-to-face interactions (human factors) are restricted due to COVID-19, or where social factors such as stricter rules of isolation (during which families spend more time together) or missed appointments interfere with daily treatment routines.

2. Materials and Methods

Adherence data were extracted on 7 June 2021 from the easypod™ connect platform for the following periods: March 2019–February 2020 (before COVID-19) and March 2020–February 2021 (during COVID-19). These time periods were selected since, in most countries (including those in this study), COVID-19 started to impact daily life from March 2020.

Of those countries (n = 35) with active patients in the easypod™ connect ecosystem, we included those that provided adherence data for ≥50 patients aged 6–18 years both before and during the pandemic. This allowed comparison of adherence before and during the pandemic using a sufficient number of school-aged patients to have a reasonable degree of precision (standard error ~0.06) for the country-specific outcomes.

Three measures of COVID-19 regulations were extracted on 27 June 2021 from the Oxford COVID-19 Government Response Tracker [20] for the period March 2020–February 2021 (during COVID-19). These included:

(i). The stringency index (SI) [21]: school closures; workplace closures; cancellation of public events; restrictions on public gatherings; closures of public transport; stay-at-home requirements; public information campaigns; restrictions on internal movements; and international travel controls. The index on any given day was calculated as the mean score of the nine indicators, each taking a value between 0 and 100 (100 = strictest). The mean SI (across all daily values) during the COVID-19 period was calculated and categorised as high (mean SI ≥ 68 (75th percentile (P75)) of SI of all countries with available data) versus medium/low (mean SI < 68).

(ii). School closure (four categories: 0—No measures, 1—Recommend closing, 2—Require closing [only at some levels or categories, e.g., just high schools, or just public schools], 3—Require closing all levels) [22]. In our study, we calculated the proportion of days during the COVID-19 period with school closure requirements at all levels (Category 3), or only at certain levels or categories, e.g., secondary or public schools only (Category 2) versus recommend closing (Category 1) or no measures (Category 0). This proportion (i.e., 100 x number of days in Category 3 or 2 divided by the total number of days during COVID-19) was then calculated and categorised as high (≥88% [P75 of all countries with available data]) versus medium/low (<88%).

(iii). Stay-at-home requirements (four categories: 0—No measures, 1—Recommend not leaving house, 2—Require not leaving house with exceptions for daily exercise, grocery shopping, and 'essential' trips, 3—Require not leaving house with minimal exceptions [e.g., allowed to leave only once every few days, or only one person can leave at a time, etc.]) [23]. In our study, we calculated the proportion of days with stay-at-home requirements including not leaving the house with minimal exceptions such as allowed to leave only once every few days, or only one person can leave at a time (Category 3), or not leaving the house with exceptions for daily exercise, grocery shopping and 'essential' trips (Category 2) versus recommend not leaving the house (Category 1) or no measures (Category 0). This proportion (i.e., 100 × number of days in Category 3 or 2 divided by the total number of days during COVID-19) was then calculated and categorised as high (≥65% (P75 of all countries with available data)) versus medium/low (<65%).

Multilevel logistic regression analyses (patient and country level) were performed, with adherence (yes/no, optimal) as the dependent variable and the main effects and interaction between period (before and during COVID-19) and either SI, required school closure, or stay-at-home requirements (fixed value per country) as the independent variable. The parameters of the interaction term were used to evaluate the impact of the regulations to the change in optimal adherence during versus before the COVID-19 period. Due to the left-skewed distribution, adherence was categorised as optimal (equivalent to missing no more than one injection per week; ≥85% of 100 × [mg of r-hGH injected/prescribed doses administered]) versus suboptimal (<85%) in the period before and during COVID-19.

Analysis was conducted in R [24]; p values <0.05 (two-sided) were considered statistically significant.

Treatment with r-hGH via easypod™ was conducted according to local practice. This real-world, retrospective analysis of the dataset was performed in accordance with the informed consent form, signed by caregivers of children and adult patients materializing their agreement for data collection, storage and use of their pseudonymised data to create aggregated statistical and general adherence reports.

3. Results

Adherence data were available for 8915 patients before the COVID-19 period and 7606 patients during the COVID-19 period from ten European countries (Czech Republic, Finland, France, Germany, Ireland, Italy, Spain, Sweden, Switzerland, UK), six South/Latin American countries (Argentina, Brazil, Chile, Colombia, Guatemala, Peru), Taiwan, and Canada. In total, data from 10599 individuals were available and 5922 patients provided adherence data both before and during the COVID-19 period.

Table 1 shows the patient demographics before and during the COVID-19 period according to country. Mean age during the selected periods was approximately 11–12 years of age and mean time on treatment halfway through the selected periods ranged between 1.0 and 4.8 years.

Table 1. Demographics for all patients before and during the COVID-19 period, by country.

Country	Before COVID-19 [a]					During COVID-19 [b]				
	N	Boys (%)	Girls (%)	Age (Years) Mean (SD)	Time on Treatment Halfway through This Period (Years) Mean	N	Boys (%)	Girls (%)	Age (Years) Mean (SD)	Time on Treatment Halfway through This Period (Years) Mean
Czech Republic	341	66	34	11.6 (3.1)	3.1	351	67	33	11.7 (3.0)	3.4
Finland	104	73	27	11.1 (3.1)	2.8	108	69	31	11.2 (3.3)	3.2
France	390	64	36	12.2 (2.7)	2.3	375	64	36	12.1 (2.8)	2.3
Germany	798	60	40	11.6 (3.1)	3.0	734	62	38	11.5 (3.1)	3.2
Ireland	74	70	30	12.1 (3.0)	1.5	76	68	32	12.5 (3.0)	2.2
Italy	281	56	44	12.2 (2.7)	1.9	282	56	44	12.3 (2.7)	2.0
Spain	2528	55	45	11.4 (2.8)	1.8	2665	54	46	11.5 (2.8)	2.0
Sweden	122	65	35	12.1 (2.9)	4.7	99	64	36	12.1 (3.1)	4.8
Switzerland	132	72	28	12.4 (3.1)	2.5	139	69	31	12.7 (3.1)	2.8
United Kingdom	540	61	39	11.6 (3.0)	2.8	513	61	39	11.8 (3.1)	3.1
Argentina	847	65	36	11.4 (2.9)	1.3	991	64	36	11.6 (2.9)	1.8
Brazil	189	60	40	11.1 (2.6)	1.4	93	60	40	11.0 (2.5)	1.8
Chile	689	57	43	11.9 (2.6)	1.5	130	52	48	12.2 (2.4)	2.2
Colombia	858	55	45	11.9 (2.6)	1.4	293	55	45	11.9 (2.7)	1.7
Guatemala	190	49	51	12.0 (2.6)	1.2	111	50	50	12.3 (2.7)	1.6
Peru	263	49	51	11.4 (2.7)	1.0	76	54	46	11.4 (2.9)	1.8
Taiwan	467	58	42	12.5 (2.3)	1.0	445	58	42	12.6 (2.2)	1.3
Canada	102	59	41	11.7 (2.9)	1.1	125	58	42	11.9 (2.8)	1.1

[a] Before COVID-19: between March 2019–February 2020; [b] During COVID-19: between March 2020–February 2021.

During the pandemic, a high mean SI as well as a high proportion of days with school closures resulted in an increase in the proportion of patients with optimal adherence to r-hGH therapy versus the pre-COVID-19 period; both $p < 0.001$, odds ratio (OR) (95% confidence interval (CI)) for SI × period: 3.8 (2.7–5.4) and 2.5 (1.8–3.6) for school closures × period. Stay-at-home requirements were not significantly related to an increase in the proportion of patients with optimal adherence ($p = 0.13$, OR (95% CI): 1.4 (0.9–2.0)) during versus before the COVID-19 period. Overall, the proportion of optimal adherence increased by 4% (from 74% to 78%) between both periods, and this was 7% (from 65% to 72%) within the countries with a high mean SI, as well as with a high proportion of days with school closures. Figure 1 shows the change in the proportion of optimal adherence over time by countries (equally weighted) with high versus medium/low regulations.

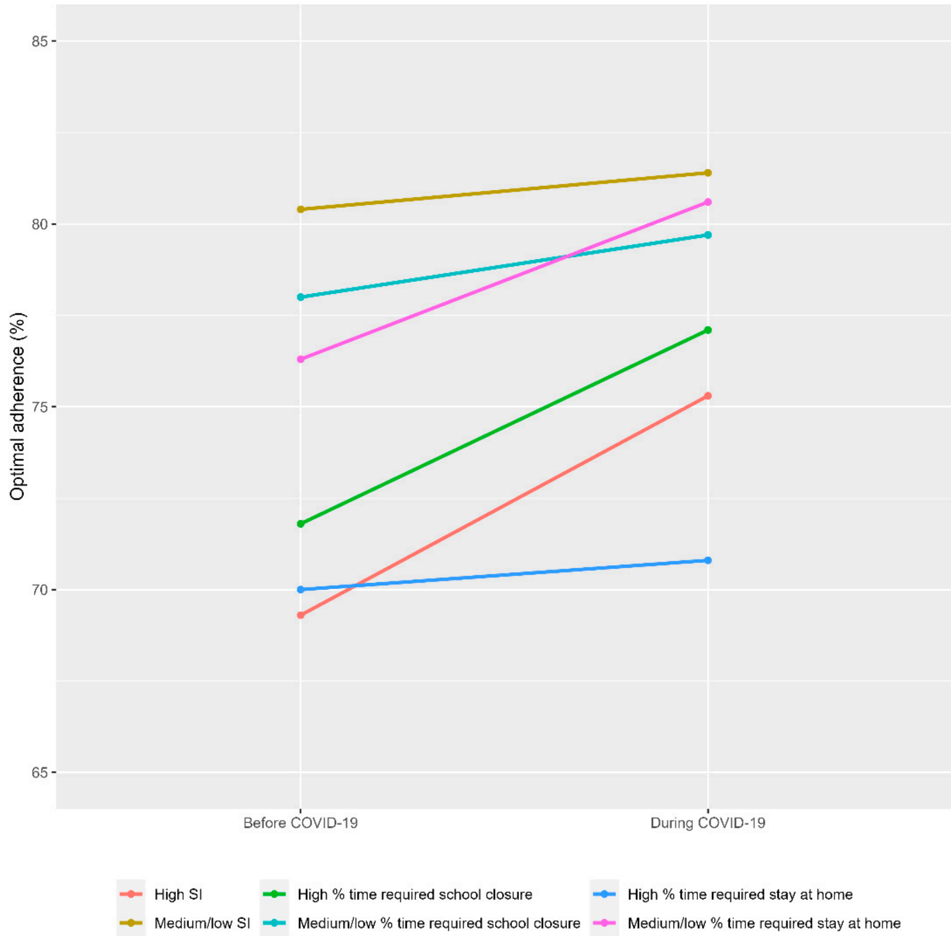

Figure 1. Change in the proportion of optimal adherence over time by countries (equally weighted) with high versus medium/low regulations.

Table 2 shows descriptive statistics of adherence before and during the COVID-19 period and the COVID-19 regulations according to country. Six of the nine countries with a high SI showed an absolute increase of >5% (range, 6 to 18%) in the proportion of patients with optimal adherence. Three South American countries, Argentina, Brazil, and Peru, with a high SI did not show a high increase (range −4 to 2%). None of the nine countries with a medium/low SI showed an increase of >5% (range, −3 to 5%). Colombia and Guatemala showed the highest increase in optimal adherence, both had a high SI and high proportion of days with required school closure but a relatively medium/low proportion of days with stay-at-home requirements.

Table 2. Adherence before and during the COVID-19 period and the COVID-19 regulations, by country.

	Before COVID-19 [a]	During COVID-19 [b]				Difference during-before
Country	**Optimal (≥85%) Adherence (%)**	**Optimal (≥85%) Adherence (%)**	**Stringency Index (Mean [SD])**	**Proportion of Time with Required School Closure (%)**	**Proportion of Time with Required Stay at Home (%)**	**Change in Optimal (≥85%) Adherence (%)**
Czech Republic	88	91	56 (18)	68	36	3
Finland	77	74	46 (14)	40	0	−3
France	83	88	64 (15)	60	52	5
Germany	80	85	64 (14)	63	36	5
Ireland	70	76	**70 (20)**	**88**	48	6
Italy	82	90	**70 (15)**	**94**	53	8
Spain	83	80	67 (13)	66	62	−3
Sweden	81	86	60 (10)	65	0	5
Switzerland	75	74	52 (13)	48	0	−1
United Kingdom	66	73	**70 (16)**	73	38	7
Argentina	62	65	**83 (16)**	**96**	**95**	2
Brazil	83	78	**68 (13)**	**97**	**82**	−4
Chile	68	74	**76 (16)**	**96**	**93**	6
Colombia	54	71	**75 (16)**	**96**	58	18
Guatemala	72	85	**71 (23)**	**96**	53	13
Peru	67	66	**80 (16)**	**97**	**96**	−1
Taiwan	69	66	25 (3)	0	0	−3
Canada	88	89	67 (13)	**96**	14	1

[a] Before COVID-19: between March 2019–February 2020; [b] During COVID-19: between March 2020–February 2021. **Bold text** = above the cut-off of P75 (68% for SI; 88% for required school closure; 65% for stay-at-home requirements).

4. Discussion

Stringent COVID-19 regulations resulted in a higher proportion of patients achieving optimal adherence to r-hGH therapy, supported by the easypod™ connect ecosystem, compared with adherence recorded before the pandemic. Overall, the proportion of patients achieving optimal adherence increased by 4% during the pandemic with a higher increase (7%) observed within the countries with a high mean SI, as well as with a high proportion of days with school closure requirements. A high SI (mean $\geq$ 68) and a high proportion of required school closure days ($\geq$88%) resulted in an increase in the proportion of patients with optimal adherence to r-hGH therapy versus the pre-COVID-19 period ($p < 0.001$). The majority of countries (six out of nine) with a high SI showed an absolute increase of >5% in the proportion of patients with optimal adherence to r-hGH treatment, while none of the countries with a medium/low SI showed an increase of >5%.

Historically, challenges affecting adherence to medication regimens include social activities and reliance upon parents/caregivers [25]. Therefore, school closure may have had a positive impact on r-hGH adherence due to decreased social activities and more parental/caregiver engagement. Within our data set (selection of patients with a 7-day regimen), we found that the proportion of days when a patient injected themselves during the COVID-19 period ranged 85–87% on Mondays to Thursdays and Sundays, and 80% on Fridays and Saturdays; this was 85–87% and 76–77% in the pre-COVID-19 period, respectively. Among patients with a 7-day regimen and a high SI during COVID-19, the proportion of days when a patient injected themselves during the COVID-19 period ranged between 83–84% on Mondays to Thursdays and Sundays, and 78–80% on Fridays and Saturdays; this was 82–84% and 73–74% in the pre-COVID-19 period, respectively. The increase in these proportions on Fridays and Saturdays may be explained by the reduced number of social activities taking place during COVID-19.

Overnight travel is also considered a major contributing factor to missed doses of r-hGH treatment, which may be due to refrigeration storage requirements [26]. Poor medication adherence has also been associated with weekends and school holidays [27]. Within our study, four South American countries (Argentina, Chile, Colombia, and Peru) had a high SI during their summer holidays and from those, three countries showed a high increase (>5%) in optimal adherence to r-hGH treatment; +8% in Argentina, +20% in Chile, and +16% in Colombia. Four (Germany, Italy, Sweden, and the United Kingdom) out of 14 countries with a medium/low SI during their summer holidays also showed a high increase in optimal adherence to r-hGH (range, 6 to 9%). Thus, during the present analysis, families residing together more often during the pandemic, without holiday periods, may have contributed to the habit of administering a daily injection when using connected digital health technologies.

The observed adherence rates to r-hGH differed among countries which may be related to a variety of socio-economic factors including cultural differences and income [28] as well as local pandemic management and adherence to introduced COVID-19 regulations. Although low- and middle-income countries largely adopted the same response strategy as high-income countries, these measures were more likely to be re-imposed in low- and middle-income countries where vaccine accessibility is poor compared with high-income countries [29]. However, the recorded adherence to COVID-19 regulations was lower in low-income countries compared with high-income countries [30]. Within our study, three South American countries (Argentina, Brazil, and Peru) had a high SI but did not show a large change in the proportion of patients with optimal adherence to r-hGH (range, −4 to 2%). When we compare the income of these countries with the other countries in our study, we found that Argentina, Brazil, and Peru had relatively lower incomes (USD 6010–8930 gross national income [GNI] per capita in 2020) [31].

To monitor compliance and inform policy decision-making, Google is continuously sharing mobility data obtained from global positioning system-enabled devices during COVID-19; data has been published for 131 countries at national and local levels for six categories such as retail, recreation, parks, and home [32,33]. Adherence to r-hGH therapy may be affected by individuals who are non-compliant with local COVID-19 regulations. Within our study, both Argentina and Peru showed relatively optimal adherence to COVID-19 regulations (residential percentage change from baseline [January/start of February 2020] was 12–19%), while Brazil showed relatively low adherence (residential percentage change from baseline was 9%), and this was similar to the countries with a medium/low SI (residential percentage change from baseline was 2–10%).

There may be several reasons for the greater increase in adherence in countries with a higher SI. The pandemic may have emphasised the need for and importance of health and the management of disease care. In addition, activity restrictions and more time at home may have strengthened the role of parents in childcare. This role has already been demonstrated in other studies [34] and the present study may confirm that parental supervision is a key factor in adherence to medical treatment.

The strengths of our study include the reliability of patients' adherence data since it was obtained from the connected ecosystem and was not self-reported, and the multi-national setting and large data set. Limitations include the fact that, when there were school closure requirements, the SI remained high (with the exception of the UK), making it difficult to investigate whether this was an important independent factor. The results could be due to other factors such as restrictions on internal movement, or a combination of variables. In addition, the number of available patients varied between countries (between 74 and 2665). This had an effect on the degree of precision of the presented proportions of optimal adherence (standard errors ranged 0.01–0.05). Furthermore, the role of variables such as age or sex could not be analysed in depth due to the sample size of some age groups in some countries. Simply combining data from all countries to measure the effect of age in combination with gender is undesirable because it does not take into account the cultural aspects of individual countries [35]. Further research with more in-depth analysis taking the cultural aspects into account may be relevant, since COVID-19 restrictions may have affected children and adolescents, and boys and girls differently [36,37]; these gender-related developmental periods may have caused different responses to parental supervision (variable social construction of childhood) [19]. Moreover, qualitative and quantitative research on the country-specific factors (such as cultural differences, health disparities, medication shortage) that impacted adherence during COVID-19 is relevant. Finally, the adherence data from January and February 2021 appeared to be incomplete for some countries because patients can upload historical injection data at any time and, it seems that for some of them, the data were not fully uploaded between March 2021 and the time when the data extraction took place (7 June 2021). However, when comparing adherence data between March–December 2019 and March–December 2020, almost similar results were shown; +3% increase in the proportion of optimal adherence, and 6% within the countries with a high SI. Furthermore, three countries (Chile, Peru and Colombia) had a much lower number of patients with adherence data during the COVID-19 period compared with before. A reason could be that this pandemic has raised concerns about safely accessing health care [38] and a post-pandemic decrease of many types of health care utilization [39]. The reasons for this observation are uncertain; it may be due to a decrease in diagnosis and a delay to the start of treatment for new patients; prolonged time between visits caused by lock down and redistribution of health care resources; prolonged time between data transmissions as HCPs and patient support programmes (PSPs) were unable to facilitate these during visits to the clinic; or whether patients interrupted or ended their treatment, for example, in cases where treatment was covered through private health care. However, we felt it was important to emphasise this disparity in health care utilization and proposed to keep these countries in the analysis. To investigate potential selection bias in these countries, we compared the proportion of patients achieving optimal adherence before COVID-19 between the group of patients who did or did not have (additional) adherence data during COVID-19. In two countries Chile and Peru), the proportion of patients achieving optimal adherence before COVID-19 was similar between the two patient groups. In Colombia, however, there was a significant difference; a higher proportion of optimal adherence before COVID-19 was observed in the group with adherence data. Further multilevel analysis showed that within the group of Colombian patients with adherence data during and before COVID-19, the proportion of optimal adherence significantly increased during versus before the COVID-19 period, after appropriate adjustment for mean time on treatment ($p < 0.001$, OR (95% CI): 484 (171–1374)). Furthermore, a limitation is that we stratified continuous, but skewed, adherence data in two categories, which reduces the amount of information available. In our study, we defined optimal adherence as an adherence rate of $\geq$85%, which is in agreement with the definition used in the largest number of studies [40]. Further analysis showed that the proportion of low adherence (defined as $\leq$56%) decreased by 1% (from 7% to 6%) between both periods, and this was a 3% decrease (from 11% to 8%) in the countries with a high mean SI, and a 2% decrease in those countries with a high proportion of days with school closures.

5. Conclusions

Automated adherence monitoring allows an insight into real-world behaviour. Data obtained can provide valuable information into patient behaviour and identify contextual factors which may affect adherence and prompt clinical intervention. Stringent COVID-19 regulations appear to have had a positive impact on the proportion of paediatric patients achieving optimal adherence to their r-hGH therapy, supported by the easypod™ connect ecosystem. While there is generally limited data concerning how COVID-19 has impacted self-management behaviours for chronic diseases, the current study, although largely hypothesis-based, shows the feasibility of adherence data to understand self-management behaviours for growth disorders during the pandemic. Treatment adherence in chronic conditions is a multifaceted issue and needs to balance the needs of the children within everyday family life. Understanding patterns of adherence can influence management strategies and help to promote adherence which benefits patients in the long term, not just during the COVID-19 pandemic. Improved adherence during this time may have been due to increased parental involvement and such engagement should be encouraged at all times and in different scenarios, including during weekends, holidays, and periods where missed injections are more likely to occur. It is hoped that the improved adherence to r-hGH observed during the pandemic, supported by the use of a connected injection device and parent/caregiver involvement, advocated by patient support programmes [34], continues. The use of digital health technologies to obtain adherence data is a useful strategy to enable HCPs to identify patients at risk of suboptimal adherence to improve clinical outcomes.

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Institutional Review Board Statement: Treatment with easypod™ was conducted according to local practice. This real-world, observational, retrospective analysis of easypod™ data was performed in accordance with the informed consent form, signed by caregivers of children and adult patients materializing their agreement for data collection, storage, and use of their pseudonymized data to create aggregated statistical and general adherence reports. The research protocol (registration no. 2021-115) was submitted to The Netherlands Organization for Applied Scientific Research (TNO) Institutional Review Board. The board approved the research proposal. In its deliberations, the board considered the research design and privacy aspects, as well as the ethical aspects and the burden and risks to the research participants.

Informed Consent Statement: Informed consent was obtained by caregivers of children and adult patients materializing their agreement for data collection, storage, and use of their pseudonymized data to create aggregated statistical and general adherence reports.

Data Availability Statement: Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck Healthcare KGaA, Darmstadt, Germany's Data Sharing Policy. All requests should be submitted in writing to Merck Healthcare KGaA. Darmstadt, Germany's data sharing portal https://www.emdgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html (accessed on 7 March 2023). When Merck Healthcare KGaA, Darmstadt, Germany has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck Healthcare KGaA, Darmstadt, Germany will endeavor to gain agreement to share data in response to requests.

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Conflicts of Interest: P.v.D. has a consultancy agreement with Merck Healthcare KGaA, Darmstadt, Germany. L.A. and Q.L.M. are employees of Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany). E.K. is an employee of Merck Healthcare KGaA, Darmstadt, Germany and holds shares in the company. R.M.B.R. has no conflict of interest to declare.

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