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Health Quality and Treatment Satisfaction in IEI Patients; Not Only IgRT but Comorbidities

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ABSTRACT

Objective: Immunoglobulin Replacement Therapy (IgRT) via intravenous (IVIG) or subcutaneous (SCIG) routes is essential for managing a large proportion of inborn errors of immunity (IEI), offering reductions in infection rates and enhancements in Health-Related Quality of Life (HRQoL) and treatment satisfaction (TS). The assessment of HRQoL and TS among a diverse spectrum of both pediatric and adult IgRT-receiving IEI patients currently needs to be expanded. The aim of this study was to investigate both HRQoL and treatment satisfaction with current clinical status in a heterogeneous group of patients with IEI receiving IVIG and SCIG.

Materials and Methods: We conducted a cross-sectional survey targeting IEI patients on IgRT, assessing TS (TSQM-9) and HRQoL (KINDL/SF-36). The survey integrated patient and caregiver perspectives with demographic, clinical, safety, and efficacy data to identify confounders of outcomes.

Results: Eighty IEI patients (ages 1-45; 55 females, 45 males) participated, with 71.2% receiving IVIG and 28.8% SCIG. HRQoL scores were significantly higher for the SCIG group compared to IVIG (p=0.006), and even more so at the 20% SCIG concentration (p=0.026). History of adverse reactions to IgRT and diagnostic delay over one year showed lower TSQM-9 scores (p=0.044 and p=0.009, respectively). Patients with comorbidities also reported lower HRQoL and TSQM-9 scores compared to their peers without comorbidities (p=0.012 and p=0.046, respectively).

Conclusion: SCIG, particularly at high concentration, shows an improvement in HRQoL outcomes, whereas adverse reactions to IgRT and diagnostic delay impair TS. Detrimental effect of IEI-related comorbidities on HRQoL and TS highlighted the critical role of timely and accurate diagnosis in IEI management.

Keywords: Health-related quality of life, home infusion therapy, intravenous immunoglobulin, patient Satisfaction, primary immunodeficiency, subcutaneous infusion

INTRODUCTION

Immunoglobulin replacement therapy (IgRT) is a medical treatment administered either intravenously (IVIG) or subcutaneously (SCIG) to restore immunoglobulin levels and reduce the frequency and severity of infections in individuals diagnosed with Inborn Errors of Immunity (IEI) (1,2). Overall, both IVIG and SCIG therapies exhibit similar clinical efficacy in IEI patients, though specific features may favor one over the other (3,4). In addition to their safety and efficacy, IgRTs are also known to contribute to heightened treatment satisfaction (TS) and improved health-related quality of life (HRQoL) for individuals with IEI (5,6).

IVIG is typically administered monthly at an infusion center or through home healthcare with a nurse. In contrast, SCIG allows patients to self-administer at home. Still,

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conventional manual rapid push of 10% SCIG requires more frequent dosing (usually weekly) and multiple infusion sites due to limited subcutaneous tissue capacity. This can impact the quality of life and adherence (7,8). To address these issues, 20% highly-concentrated pump-assisted SCIG and Recombinant human hyaluronidase (rHuPH20)-facilitated pump-assisted SCIG (fSCIG) have been developed. These options allow for less frequent dosing (every two to four weeks) and fewer infusion sites, improving treatment convenience and adherence (9-12).

In studies investigating the factors affecting HRQoL and TS in IEI patients, the focus has generally been on evaluating specific IEI subgroups as Predominantly Antibody Deficiency (PAD) (13,14). Furthermore, research on the impact of IgRT methods on HRQoL and TS has predominantly been based on the switch from IVIG to SCIG, highlighting an improvement in HRQoL and TS compared to baseline (13,15,16). An integrated assessment of Health-Related Quality of Life (HRQoL) and Treatment Satisfaction (TS) within a population of individuals with IEI, spanning various age groups from children to adults, undergoing Immunoglobulin Replacement Therapy (IgRT), across different phenotypic categories, remains to be conducted. Thus, the current study aims to assess the HRQoL and TS of such IEI patients receiving IgRT and identify the factors influencing these outcomes.

MATERIALS and METHODS

The study was conducted between 30 September 2022 and 15 September 2023 at the Pediatric Immunology Clinic of Marmara University Faculty of Medicine. Ethical approval was received from the Marmara University Ethics Committee (Protocol ID: 09.2022.842) and written informed consent was duly obtained from the patients and parents.

Patients between the ages of 1 to 45 years who had been diagnosed with IEI according to the International Union of Immunological Societies (IUIS) and the Middle East and North Africa Diagnosis and Management Guidelines were enrolled (17,18). We included patients followed at our tertiary clinic who had been receiving IVIG or SCIG for a minimum of one year and who had no active infection at the time of evaluation. Patients who did not provide consent for participation and those who had changes in the IgRT route in-between subcutaneous and intravenous in the last 1 year were excluded from the study.

Data Collection

The demographic, clinical, and laboratory data of the patients were recorded from medical records.

The IgRT dose was standardized and recorded for all patients by calculating the gram dose per kilogram per 21 days. Additionally, route of IgRT administration (intravenous, subcutaneous), patient practices (dosage, frequency of administration), IgRT-related local and systemic reactions, and serum trough/steady IgG levels were recorded.

Questionnaires for Health-Related Quality of Life and Treatment Satisfaction

HRQoL of life was evaluated by using both the Kinder Lebensqualitätsfragebogen: Children's Quality of Life Questionnaire (KINDL) child survey for the patients aged 4-18 years and the relevant KINDL parent questionnaires, previously validated for Turkish children (19). For child participants with intellectual disability or those unable to comply with the questionnaire, only the KINDL-Parent questionnaire was administered to assess their quality of life. The HRQoL of life in the adult participants was assessed using the Short Form Health Survey (SF-36) questionnaire. All adult and pediatric participants' treatment satisfaction was assessed by administering the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) to the patients or parents. The TSQM-9 questionnaire was administered to the parents for patients younger than 12 years old or patients with intellectual disability. All other patients answered the questionnaire themselves. The KINDL, SF-36, and TSQM-9 surveys were administered and calculated as described in previous studies (19-22). The items, subscales and score calculation methods for all questionnaires are presented in the supplementary material.

Statistical Analysis

Statistical analysis was conducted by Jamovi 2.3.26 version (The Jamovi Project, Australia). Continuous variables between groups were compared with the Mann-Whitney U test. The categorical variables between groups were compared using the chi-square test. A *p*-value below 0.05 was considered statistically significant within a 95% confidence interval. Graphs are produced by GraphPad Prism 9 (GraphPad Software Inc., San Diego, California).

Table I: Demographic and Clinical Characteristics of Patients

	n=80 (100%)
Age (years), median (IQR)	10.1 (6.2-15.6)
<18 years, n (%)	63 (78.7)
≥ 18 years, n (%)	17 (21.3)
Age at symptom onset (years), median (IQR)	0.5 (0-1)
Age at diagnosis (years), median (IQR)	3.5 (1-7)
Diagnostic delay (years), median (IQR)	2 (1-5)
≤1 year, n (%)	37 (46)
>1year, n (%)	43 (54)
IgRT route	
IVIG	57 (71)
SCIG	23 (29)
SCIG 10% (Conventional) (manual)	9 (11)
SCIG 20% (High Concentration) (pump-assisted)	11 (14)
fSCIG 10% (pump-assisted)	3 (4)
IgRT-related adverse reactions, n (%)	46 (58)
IVIG (Systemic)	12 (21)
Fever	6 (11)
Urticaria	5 (9)
Vomiting	2 (3)
Anaphylaxis	1 (2)
SCIG	10 (45)
Systemic	1 (5)
Myalgia	1(5)
Local	10 (45)
Erythema	6 (26)
Swelling	6 (26)
Pain	5 (22)
Itching	4 (17)
IgRT dose (gr/kg/every three weeks) median (IQR)	0.445 (0.380-0.500)
Serum IgG (mg/dl/), median (IQR)	1141 (850-1485)
Infections[a] (times/year), median (IQR)	1.5 (0-3)
Antibiotics prescribed	1 (0-2)
Pneumonia*	0 (0-0)
URTI*	0.5 (0-2)
Hospitalization (days/year)	0 (0-0)
School/work attendance, n (%)	50 (62)
School/work absence (days/year), median (IQR)	7 (0-27)

IEI: Inborn errors of immunity, **IgRT:** Immunoglobulin replacement therapy, **IQR:** Interquartile range, **IVIG:** Intravenous immunoglobulin, **fSCIG:** Facilitated SCIG, **SCIG:** Subcutaneous immunoglobulin, **URTI:** Upper respiratory infections, *, diagnosed and treated infections as per physician's assessment.

RESULTS

Patient Characteristics

A total of eighty patients were included in the study. The demographic and clinical characteristics of the participants are summarised in detail in Table I and Figure 1A.

Concerning the IEI category, the distribution of diagnosis was as follows: combined immunodeficiency (CID) constituted 65% (n=52), predominantly antibody deficiency accounted for 28.8% (n=23), diseases of immune dysregulation comprised 5% (n=4), and phagocyte defects 1.2% (n=1; Dursun Syndrome due to Glucose-6-Phosphatase Catalytic Subunit 3 deficiency). Of the 52 patients diagnosed with CID, 67% (n=35) were diagnosed with syndromic CID while 33% (n=17) were diagnosed with CID generally less profound than severe combined immunodeficiency. Among our cohort, 71% (n=57) were receiving IVIG, 11% (n=9) 10% SCIG (conventional), 14% (n=11) 20% high-concentration SCIG, and 4% (n=3) fSCIG replacement therapies.

Additionally, the SCIG group was compared to the IVIG group for the infection rates, serum IgG levels, and number of days of school/work absence in the last year. No significant differences were observed between the two groups regarding the median (IQR 25-75%) infection frequency; SCIG group at 1 (IQR 1-3) vs the IVIG group at 2 (IQR 0-3) and IgG levels; SCIG group at 1056 (IQR 657-1366) vs the IVIG group at 1147 (IQR 954-1556) (p=0.704 and p=0.123 respectively). The annual school and work absenteeism in the SCIG group was significantly lower at 6 (IQR 0-10) compared to the IVIG group at 20 (IQR 17-30) (p<0.001).

Health-Related Quality of Life and Treatment Satisfaction Surveys

TS was evaluated in all patients (100%), while HRQoL was assessed in 88% of the participants. To ascertain the HRQoL for pediatric patients with IEI, the KINDL questionnaire was utilized, with parents of 92% of children completing the KINDL-Parent survey and 71% of children responding to the KINDL-Child version. The median total score for the KINDL-Child was 66.7, with an IQR of 56 to 76.5, while the KINDL-Parent reflected a median score of 68.3 (IQR 57.4-76.1). Within the subscales of KINDL, the disease-related questions yielded the lowest scores for both children (median 58.3, IQR 41.7-75) and parents (median

60.4, IQR 45.8-75). Conversely, the highest scores were recorded in the family subscale, with a median of 81.3 (IQR 75-100) for children and 87.5 (IQR 70.3-93.8) for parents, indicating consistency across respondents. Furthermore, the analysis revealed no significant statistical differences between the KINDL-Child and KINDL-Parent total and subscale scores. Consequently, the KINDL-Parent scores were adopted as the primary measure for evaluating HRQoL in children with IEI (Figure 1B).

Out of the seventeen adult patients, 65% of them were able to respond to the SF-36 questionnaire. This was primarily attributed to intellectual disability, with 4 of them having Ataxia-Telangiectasia and 2 with Combined Immune Deficiency who were unable to respond. The SF-36 survey, which assesses HRQoL in adult patients with IEI, revealed a median total score of 77.8 (IQR 52.8-85.7). The vitality subscale which assesses the level of energy or fatigue scored the lowest with a median of 60 (IQR 50-62.5), while the highest medians were observed in the physical role limitations and bodily pain subscales, both at a median of 100 (IQR 49.5-100) and 100 (IQR 75-100) respectively (Figure 1C).

When evaluating treatment satisfaction through TSQM-9, the total score showed a median of 74 (IQR 66-84). The effectiveness subscore presented a median of 77.8 (IQR 66.7-95.8), the convenience subscore a median of

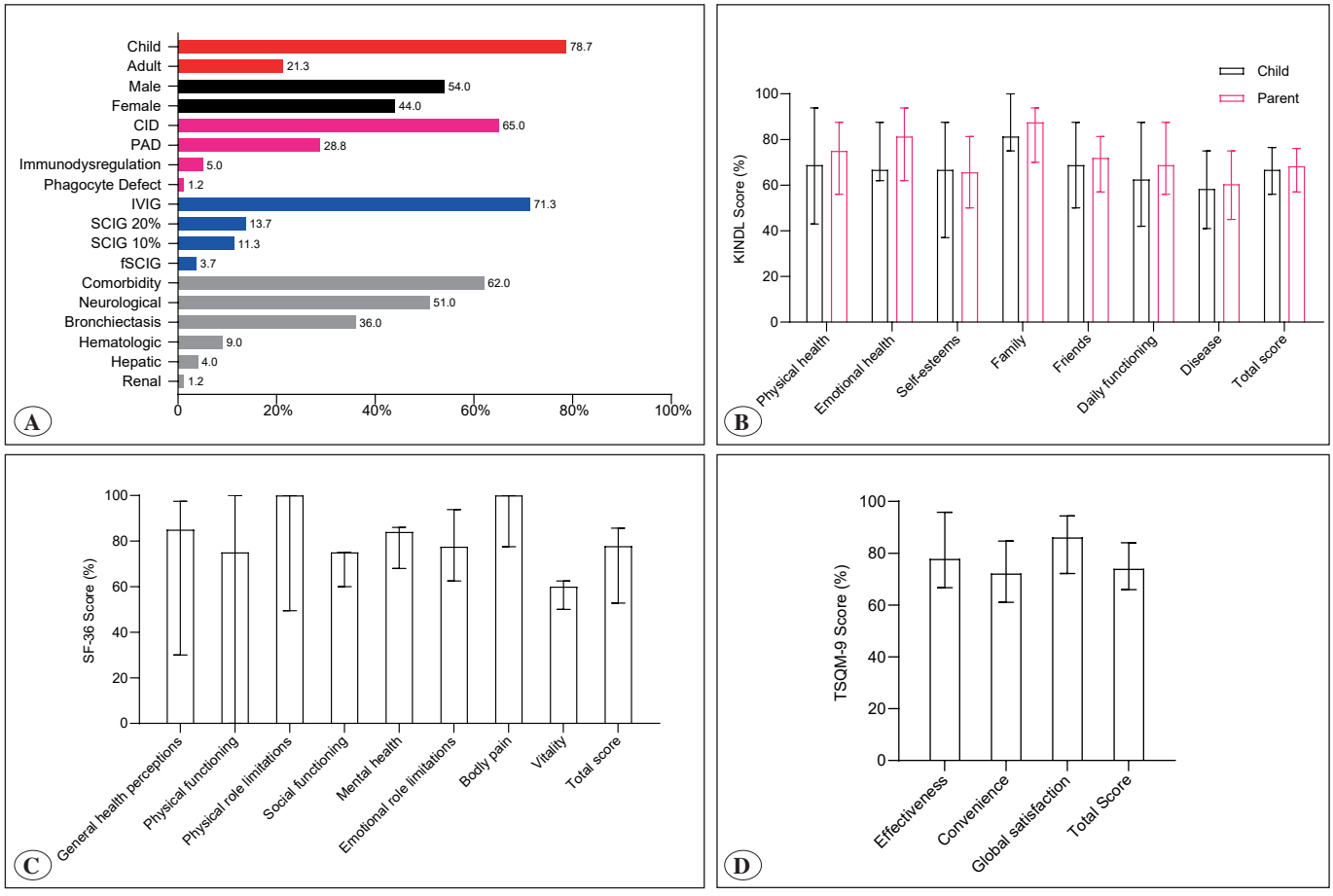

Figure 1. A) Demographic and clinical characteristics of IEI patients receiving IgRT, **B)** Comparison of KINDL-Child and KINDL-Parent total and subscale scores, **C)** SF-36 total and subscale scores for HRQoL surveys, **D)** TSQM-9 total and subscale scores for TS surveys.

The scores are presented as median (IQR 25-75%)

fSCIG: Facilitated subcutaneous immunoglobulin, **HRQoL:** Health-related quality of life, **IEI:** Inborn errors of immunity, **IQR:** Interquartile range, **IVIG:** Intravenous immunoglobulin, **KINDL:** Kinder Lebensqualitätsfragebogen: Children's Quality of Life Questionnaire, **PAD:** Predominantly antibody deficiency, **CID:** Combined immunodeficiency, **SCIG:** Subcutaneous immunoglobulin, **SF-36:** Short Form Health Survey-36, **TS:** Treatment Satisfaction, **TSQM-9:** Treatment Satisfaction Questionnaire for Medication-9

Table II: Factors Influencing Health Related Quality of Life and Treatment Satisfaction in Patients with Inborn Errors of Immunity Receiving Immunoglobulin Replacement Therapy.

		HRQoL%			TS %		
		n=70 (100%)	Median (IQR)	p value	n=80 (100%)	Median (IQR)	p value
Sex	Female	30 (43)	67.7 (56.2-74.4)	0.280	35 (44)	74 (63-84)	0.361
	Male	40 (57)	72.2 (57.4-83.0)		45 (56)	76 (70-82)	
Child/Adult	Child	58 83)	68.2 (57.4-76.1)	1.000	63 (79)	74 (69-84)	0.532
	Adult	12 (17)	69.6 (52.8-85.7)		17 (21)	74 (62-88)	
IgRT route	IVIG	48 (68)	64.4 (55.7-73.5)	**0.006***	57 (71)	74 (66-82)	0.643
	SCIG	22 (32)	74.7 (67.9-85.3)		23 (29)	74 (66-88)	
SCIG concentration	10%	11 (16)	68.0 (60.3-73.9)	**0.026***	12 (15)	70 (63-80)	0.075
	20%	11 (16)	84.5 (74.1-84.2)		11 (14)	88 (72-91)	
Adverse reaction with IgRT	presence	28 (40)	68.0 (59.8-79)	0.649	34 (43)	73 (63-80)	**0.044***
	absence	42 (60)	68.3 (56.4-80.4)		46 (57)	79 (70-86)	
Diagnosis	CID	46 (66)	64.9 (56.3-78.6)	0.138	52 (65)	74 (64-82)	0.162
	Non-CID	24 (34)	73.5 (62.9-80.1)		28 (35)	76 (72-86)	
Diagnosis	PAD	20 (28)	73.8 (69.0-85.0)	0.054	23 (29)	76 (72-88)	0.174
	Non-PAD	50 (72)	64.6 (56.4-76.1)		57 (71)	74 (64-82)	
Diagnostic delay (years)	≤1	31 (44)	68.5 (58.3-73.8)	0.692	37 (46)	80 (74-84)	**0.009***
	>1	39 (56)	68.2 (55.4-84.8)		43 (54)	70 (62-81)	
Comorbidity	presence	43 (61)	63.8 (54.5-84)	**0.012***	50 (62)	74 (62-82)	**0.046***
	absence	27 (39)	73.5 (64.3-84)		30 (38)	78 (72-85)	

HRQoL: Health-related quality of life, **IgRT:** Immunoglobulin replacement therapy, **IQR:** Interquartile range, **IVIG:** Intravenous immunoglobulin, **PAD:** Predominantly antibody deficiency, **SCIG:** Subcutaneous immunoglobulin, **CID:** Combined immunodeficiency, **TS:** Treatment satisfaction. *p<0.05, Mann-Whitney U test

72.2 (IQR 61.1-84.7), and the global satisfaction subscore a median of 86.1 (IQR 72.2-94.4) (Figure 1D).

Comparison of HRQoL and TS between groups

Patients were categorized into sub-groups based on criteria that may affect these two outcomes: sex, age, method of IgRT administration, the concentration of SCIG (10% and 20%), presence or absence of IgRT-related adverse reactions, diagnosis of CID or non-CID, diagnosis of PAD or non-PAD, diagnostic delay over one year or less, and the presence or absence of comorbidities. The surveys of HRQoL and TSQM-9 scores were compared between these groups, with the results presented in Table II, Figure 2A and Figure 2B.

When HRQoL was evaluated depending on IgRT route in pediatric participants, a significant difference was observed in KINDL-P median scores between SCIG and IVIG groups 75.1 (IQR 72.6-85.4) vs. 64 (IQR 56-72), p<0.001).

Subscales of HRQoL and TS

Further comparisons were performed to investigate the subscales contributing to the observed differences in HRQoL between the IVIG and SCIG groups. The median KINDL-Parents' subscales score of SCIG vs IVIG for self-esteem subscale was 81.3 (IQR 68.8-87.5) vs 56.3 (IQR 37.5-68.8), for friends subscale was 75.0 (IQR 68.8-93.8) vs 68.8 (IQR 50.0-81.3), and for the disease subscale was 66.7 (IQR 58.3-95.8) vs 58.3 (IQR 45.8-68.9) (p<0.01, p=0.015, p=0.030, respectively) (Figure 2C). The comparison of HRQoL subscales between the 20% and 10% SCIG groups revealed a significant difference only in the KINDL-Parents' family subscale, with a median of 93.8 (IQR 78.1-100) in the 20% SCIG group and 75 (IQR 71.8-87.5) in the 10% SCIG group (p=0.035). Participants with and without comorbidities revealed no significant difference in HRQoL subscales.

For the TSQM-9 subscales, we detected a significant difference only in the effectiveness subscale with a me-

dian effectiveness subscale of 66.7 (IQR 61.1-81.9) in the group with IgRT adverse reactions and the group without adverse reactions of 83.3 (IQR 68.3-100) (p=0.015). Moreover, individuals experiencing a diagnostic delay exceeding one year showed significantly lower median values in the effectiveness subscale (66.7, IQR 61.1-83.3) compared to those with a delay of one year or less (88.9, IQR 73.8-100) (p<0.001). Similarly, the median of the general satisfaction subscale was significantly lower in the group with a diagnostic delay exceeding one year (80.6, IQR 72.2-88.9) compared to the group with a delay of one year or less (88.9, IQR 83.3-94.4) (p=0.006). Participants with and without comorbidities revealed no significant difference in TSQM-9 subscales, Despite the lack of a significant difference in TSQM-9 total scores between the IVIG and SCIG groups based on the IgRT treatment method, the convenience sub-scale had a median of 66.7 (IQR 55.6-77.8) in the IVIG group, which was significantly lower than the SCIG group's score of 83.3 (IQR 69.4-100) (p: 0.002) (Figure 2D).

DISCUSSION

This study explored the determinants of HRQoL and treatment satisfaction among 80 IEI patients undergoing IgRT. We found that the lowest HRQoL scores in pediatric patients were reported in the disease subscale, whereas in adults, the greatest challenges were observed in the vitality subscale. Conversely, the highest HRQoL scores were noted in the family relationships subscale in children but the physical role limitations and bodily pain subscales in adults. Current findings confirmed that patients receiving SCIG at home reported higher HRQoL scores than those receiving IVIG in a hospital setting. Furthermore, a 20% concentration of SCIG was associated with improved HRQoL in comparison to a 10% concentration. Previous studies also suggested that higher concentration SCIG formulations contribute to enhanced HRQoL, a finding that aligns with the patterns observed in our study cohort (23-25). Moreover, despite variations in HRQoL outcomes across different cohorts and measurement tools, a consistent observation is the beneficial effect of SCIG on individuals' perceptions of general health and family relationship domains. These domains typically reflect higher scores, underscoring SCIG's positive influence on aspects of daily life and interpersonal connections (26-28). In the current study, the family relationships subscale had the highest scores in both the IVIG and SCIG groups, which meant receiving SCIG at home did not cause a difference in this aspect. In similar studies evaluating pediatric participants using questionnaires that included the self-esteem subscale, it was found that there was no difference in self-esteem when comparing SCIG to IVIG (13,16). On the contrary, the findings in our cohort exhibited that the SCIG group had higher scores not only in the general health perception domain but also in the social domains compared to IVIG. The utilization of SCIG infusions through home-based administration demonstrated a notable reduction in the loss of school or workdays and probably made an additional favourable impact on social issues in our cohort.

Home-based IgRT therapies, regardless of the infusion route (IV/SC), are known to offer higher treatment satisfaction and preference over hospital-based IgRT, with SCIG treatment being favoured due to its lower systemic side effects, reduced school and work absenteeism, less fluctuating IgG levels, and ease of self-administration compared to IVIG (5,13,27,29,30). However, in pediatric patients, especially those under the age of 5, there is a tendency among parents and caregivers to prefer IVIG over SCIG (31). The primary factors driving the preference of patients who opt for IVIG have been identified as apprehension related to self-infusion and anxieties about the potential side effects when administered at home (29,31). In a recent study that compared the TSQM-9 subscales with the IgRT method, SCIG at home was associated with high convenience and effectiveness compared to IVIG. High effectiveness was reported to be achieved by high serum IgG levels (32). In our cohort, IgG levels were similar in the IVIG and SCIG groups; therefore, the similarity in TS total scores between IVIG and SCIG is unsurprising. In addition, TSQM-9 total scores, effectiveness, and global satisfaction subscales were similar in both IVIG and SCIG groups. However, the convenience subscale of TSQM-9 was higher in the SCIG group than the IVIG group, and the number of days absent from school/work was lower in the SCIG group. In this context, the higher subscale of convenience for TS provided by SCIG may be associated with the independence offered to patients by allowing self-administration in the home environment.

We also observed that a delay in diagnosis and a history of adverse reactions to IgRT of more than one year correlated with lower treatment satisfaction as measured by the TSQM-9. Reduced TS in the presence of IgRT-related adverse reactions has been reported previously (27,33). However, TSQM-9 subscales demonstrated diminished scores for the effectiveness domain, with no differences in convenience and overall satisfaction in relation to adverse reactions. This might be attributed to the fact that

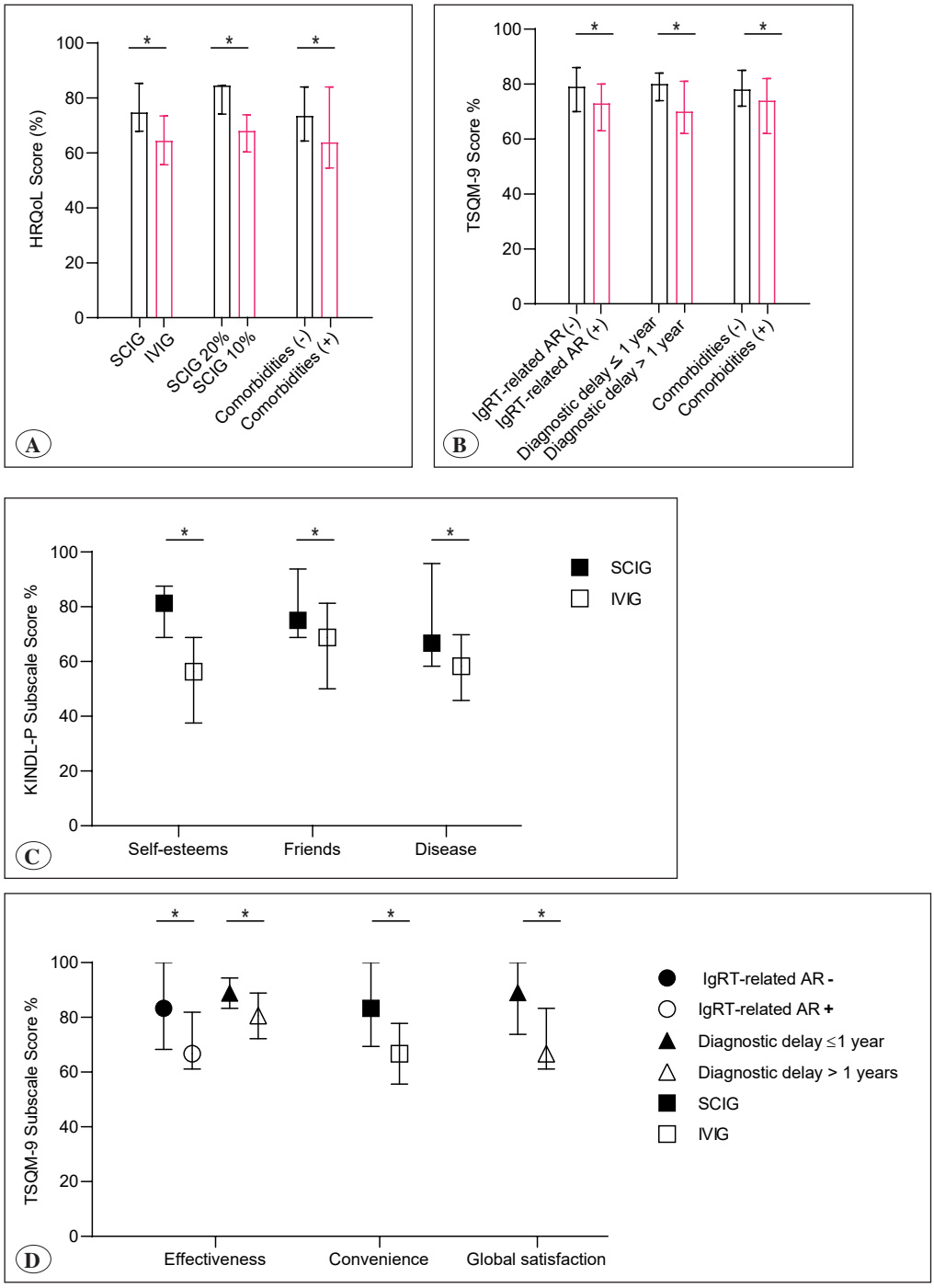

Figure 2. A) KINDL-Parent and SF-36 surveys pooled for HRQoL among IEI patients when sub-grouped by IgRT route; IVIG vs SCIG, SCIG concentration; 10% vs 20%, comorbidity; with or without. **B)** TSQM-9 survey for TS among IEI patients when sub-grouped by IgRT-related adverse reactions; (+) or (-), diagnostic delay; ≤1 or > 1 years, comorbidity; (+) or (-), **C)** KINDL-Parent subscales surveys among IEI patients when sub-grouped by IgRT route; IVIG vs SCIG, **D)** TSQM-9 subscales surveys among IEI patients when sub-grouped by IgRT-related adverse reactions; (+) or (-), diagnostic delay; ≤1 or >1 year.

The scores are presented as median (IQR 25-75%) *p<0.05, Mann-Whitney U test.

AR: Adverse reaction, **HRQoL:** Health-related quality of life, **IEI:** Inborn errors of immunity, **IgRT:** Immunoglobulin replacement therapy, **IQR:** Interquartile range, **IVIG:** Intravenous immunoglobulin, **KINDL:** Kinder Lebensqualitätsfragebogen: Children's Quality of Life Questionnaire, **SCIG:** subcutaneous immunoglobulin, **SF-36:** Short Form Health Survey-36, **TS:** Treatment Satisfaction, **TSQM-9:** Treatment Satisfaction Questionnaire for Medication-9.

TSQM-9 does not have a specific domain related to drug adverse reactions. It is well-established that diagnostic delay adversely affects HRQoL, particularly in adult patients and those diagnosed with PAD (34). In our study, the lack of impact of diagnostic delay on HRQoL scores is attributed to the majority of our cohort comprising pediatric patients, the relatively favorable median diagnostic delay duration of 2 years, and the presence of a heterogeneous diagnostic diversity among participants. The observed association between lower diagnosis delay and higher treatment satisfaction supports the reports of increased treatment satisfaction with long-term IgRT, independent of the administration route (35,36). Furthermore, the presence of comorbidities exhibited a detrimental impact on both HRQoL and TS in current patient group, thereby reinforcing the congruence with existing datasets (14,33,34).

In conclusion, for IEI patients who receive the optimal dose of IgRT and achieve the target biological IgG levels, SCIG and 20% SCIG treatment offers higher HRQoL among the routes. This improvement is attributed to the self-administration capability of SCIG at home, fostering independence and diminishing school/work absenteeism days. Nevertheless, factors influencing treatment satisfaction and preference extend beyond these aspects. In the context of IEI patients undergoing IgRT, satisfaction is bolstered by a regime that minimizes diagnostic delays and IgRT-related adverse reactions throughout an extended treatment duration. Furthermore, IEI patients where comorbidities can be prevented during outcome are associated with a more favorable HRQoL and TS. As confirmed hereby, in addition to IgRT modalities, the clinical characteristics of patients with IEI exert a significant influence on both HRQoL and TS.

Conflict of Interest

All authors certify that they have no conflicts of interest to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship Contributions

Concept: **Melek Yorgun Altunbas, Sevgi Bilgic Eltan, Safa Baris, Ahmet Ozen, Elif Karakoc-Aydiner,** Design: **Melek Yorgun Altunbas, Sevgi Bilgic Eltan, Safa Baris, Ahmet Ozen, Elif Karakoc-Aydiner,** Data collection or processing: **Melek Yorgun Altunbas, Ezgi Yalcin Gungoren, Asena Pinar Sefer, Royala Babayeva, Salim Can,** Analysis or Interpretation: **Melek Yorgun Altunbas, Ezgi Yalcin Gungoren, Asena Pinar Sefer, Royala Babayeva, Elif Karakoc-Aydiner,** Literature search: **Melek Yorgun Altunbas, Ezgi Yalcin Gungoren, Elif Karakoc-Aydiner,** Writing: **Melek Yorgun Altunbas, Sevgi Bilgic Eltan, Safa Baris, Ahmet Ozen, Elif Karakoc-Aydiner,** Approval: **Melek Yorgun Altunbas, Ezgi Yalcin Gungoren, Asena Pinar Sefer, Royala Babayeva, Salim Can, Sevgi Bilgic Eltan, Safa Baris, Ahmet Ozen, Elif Karakoc-Aydiner.**

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SUPPLEMENTARY FILE

Health Quality and Treatment Satisfaction in IEI Patients; Not Only IgRT, But Comorbidities

Altunbas MY et al.

Characteristics and Calculations of Questionnaires

1. KINDL^R QUESTIONNAIRES

Three versions of the KINDL^R questionnaire are available as self-report measures for different age groups;

Kiddy-KINDL^R for children aged 4 to 6

Kid-KINDL ^{R} for children aged 7 to 13

Kiddo-KINDL^R for adolescents aged 14 to 17

In addition, the questionnaire is available in two proxy versions for parents (3-6-year-olds and 7-17-year-olds):

Kiddy-KINDL^R for Parents of children aged 3 to 6

Kid-/Kiddo-KINDL^R for parents of children and adolescents aged 7-17

The KINDL^R questionnaire consists of 24 Likert-scaled items associated with six dimensions: physical well-being, emotional well-being, self-esteem, family, friends, and everyday functioning (school or nursery school/kindergarten). The sub-scales of these six dimensions can be combined to produce a total score. All versions of the KINDL^R contain an additional sub-scale entitled "Disease", whose items can be completed in case of prolonged illness or hospitalization. The additional sub-scale consists of a filter question and six items which measure the child's quality of life with respect to his or her illness.

On account of the particular difficulties associated with interviewing young children, the structure of the Kiddy-KINDLR differs from that of the other questionnaires (Kid/Kiddo). In the self-report version, it only consists of twelve items, two for each dimension. This means that no sub-scale scores can be calculated for the individual dimensions but only a total score. The additional questions on "Disease" are, on the other hand, included in full. The response categories of the Kiddy-KINDL^R cover 3 levels (1 = never, 2 = sometimes, 3 = very often), the children are to be questioned in a face-to-face interview. The parents' version of the Kiddy-KINDL^R with its 24 items in 6 dimensions corresponds in structure to the parents' version of the KINDL^R for 7 to 17-year-old children and teenagers. However, in order to make up for the potentially lower information content of the self-reported responses by young children, the parent's version of the Kiddy-KINDL^R contains a further 22 items which can be treated as a sub-scale in their own right.

1.1 Structure of the Sub-Scales and Classification of Items

1.1.1 Self-report versions

Kiddy-KINDLR (4 to 6-year-olds)	**Kid-KINDLR** (7 to 13-year-olds)	**Kiddo-KINDLR** (14 to 17-year-olds)
Children's Version (Interview)	Children's Version	Teenagers' Version
	Physical Well-Being	
1..... I felt ill	1..... I felt ill	1..... I felt ill
2..... I had a headache or tummy-ache	2..... I had a headache or tummy-ache	2..... I was in pain
	3..... I was tired and worn-out	3..... I was tired and worn-out
	4..... I felt strong and full of energy	4..... I felt strong and full of energy
	Emotional Well-Being	
3..... I had fun and laughed a lot	5..... I had fun and laughed a lot	5..... I had fun and laughed a lot
4..... I was bored	6..... I was bored	6..... I was bored
	7..... I felt alone	7..... I felt alone
	8..... I was scared	8..... I felt scared or unsure of myself

Self-Esteem		
5..... I was proud of myself	9..... I was proud of myself	9..... I was proud of myself
6..... I felt pleased with myself	10..... I felt on top of the world	10..... I felt on top of the world
	11..... I felt pleased with myself	11..... I felt pleased with myself
	12..... I had lots of good ideas	12..... I had lots of good ideas
Family		
7..... I got on well with my parents	13..... I got on well with my parents	13..... I got on well with my parents
8..... I felt fine at home	14..... I felt fine at home	14..... I felt fine at home
	15..... We quarrelled at home	15..... We quarrelled at home
	16..... My parents stopped me from doing certain things	16..... I felt restricted by my parents
Friends		
9..... I played with friends	17..... I played with friends	17..... I did things together with my friends
10..... I got along well with my friends	18..... Other kids liked me	18..... I was a "success" with my friends
	19..... I got along well with my friends	19..... I got along well with my friends
	20..... I felt different from other children	20..... I felt different from other people
Everyday Functioning (School or Nursery School/Kindergarten)		
11..... I coped well with the assignments set in nursery school/kindergarten	21..... doing my schoolwork was easy	21..... doing the schoolwork was easy
	22..... I enjoyed my lessons	22..... I found school interesting
12..... I enjoyed nursery school/ kindergarten	23..... I worried about my future	23..... I worried about my future
	24..... I worried about bad marks or grades	24..... I worried about getting bad marks or grades
"Disease" Module		
13. Are you staying in hospital just now or do you have some long-term illness? (Filter question)	25. Are you staying in hospital just now or do you have some long-term illness? (Filter question)	25. Are you staying in hospital just now or do you have some long-term illness? (Filter question)
14.... I was afraid that my illness might get worse	26.... I was afraid that my illness might get worse	26.... I was afraid that my illness might get worse
15.... I was sad because of my illness	27.... I was sad because of my illness	27.... I was sad because of my illness
16.... I was able to cope well with my illness	28.... I was able to cope well with my illness	28.... I was able to cope well with my illness
17.... my parents treated me like a baby because of my illness	29.... My parents treated me like a baby because of my illness	29.... My parents treated me like a baby because of my illness
18.... I avoided others to notice my illness	30.... I wanted nobody to notice my illness	30.... I wanted nobody to notice my illness
19.... I missed something at nursery school/kindergarten because of my illness	31.... I missed something at school because of my illness	31.... I missed something at school because of my illness

1.1.2 Parents' versions

Kiddy-KINDLR (3 to 6-year-olds)	**KINDLR** (7 to 17-year-olds)
Parents' Version	Parents' Version
Physical Well-Being	
1.....my child had fun and laughed a lot	1. … my child felt ill
2. … my child had a headache or tummy-ache	2. … my child had a headache or tummy-ache
3.....my child was tired and worn-out	3.....my child was tired and worn-out
4.....my child felt strong and full of energy	4.....my child felt strong and full of energy
Emotional Well-Being	
5.....my child had fun and laughed a lot	5.....my child had fun and laughed a lot
6.....my child didn't feel much like doing anything	6.....my child didn't feel much like doing anything
7.....my child felt alone	7.....my child felt alone
8.....my child felt scared or unsure of her-/ himself	8.....my child felt scared or unsure of itself
Self-Esteem	
9.....my child was proud of him-/herself	9.....my child was proud of himself
10.... my child felt on top of the world	10.... my child felt on top of the world
11.... my child felt pleased with him-/ herself	11.... my child felt pleased with him-/herself
12.... my child had lots of good ideas	12.... my child had lots of good ideas
Family	
13.... my child got on well with us as parents	13.... my child got on well with us as parents
14.... my child felt fine at home	14.... my child felt fine at home
15.... we quarrelled at home	15.... we quarrelled at home
16.... my child felt that I was bossing him/her around	16.... my child felt that I was bossing him around
Friends	
17.... my child played with friends	17.... my child did things together with friends
18.... my child was liked by other kids	18.... my child was liked by other kids
19.... my child got along well with his friends	19.... my child got along well with his/her friends
20.... my child felt different from other children	20.... my child felt different from other children
Everyday Functioning (School or Nursery School/Kindergarten)	
21.... my child coped well with the assignments set in nursery school/ kindergarten	21.... my child easily coped with schoolwork
22.... my child enjoyed the nursery school/ kindergarten	22.... my child enjoyed the school lessons
23.... my child looked forward to nursery school/kindergarten	23.... my child worried about his future
24.... my child made lots of mistakes when doing minor assignments or homework	24.... my child was afraid of bad marks or grades
"Disease" Module	
47. Is your child staying in hospital just now or does it have a long-term illness? (Filter question)	25. Is your child staying in hospital just now or does it have a long-term illness? (Filter question)
48.....my child was afraid that the illness might get worse	26.....my child was afraid that the illness might get worse
49. … my child was sad because of the illness	27. … my child was sad because of the illness
50.....my child was able to cope well with his illness	28.....my child was able to cope well with his illness
51.....we treated our child as though he/she were younger, because of the illness	29.....we treated our child as though he were younger, because of the illness
52.....my child avoided others to notice his illness	30.....my child avoided others to notice his illness
53.....my child missed something at nursery school/kindergarten because of his illness	31.....my child missed something at school because of his illness

Kiddy-KINDLR (3 to 6-year-olds)
Parents' Version
Additional Items "Kiddy Parents"
25..... my child was moody and whined a lot
26..... my child had a healthy appetite
27..... I managed to show patience and understanding towards my child
28..... my child felt under pressure
29..... my child slept soundly
30..... my child romped around and was very active
31..... my child kept bursting into tears
32..... my child was cheerful and in a good mood
33..... my child was alert and able to concentrate well
34..... my child was easily distracted and absent- minded
35..... my child enjoyed being with other children
36..... I had to give my child a telling-off
37..... I praised my child
38..... my child had problems with teachers, kindergarten staff or other child-minders
39..... my child was nervous and fidgety
40..... my child was lively and energetic
41..... my child complained of being in pain
42..... my child was sociable and out- going
43..... my child succeeded at everything he set out to do
44..... my child became dissatisfied easily
45..... my child cried bitterly
46..... my child lost his temper quickly

1.1.3. Validated Turkish Questionnaires

1.1.3.1 Self-report versions

Kiddy-KINDLR (4 to 6-year-olds)	**Kid-KINDLR** (7 to 13-year-olds)	**Kiddo-KINDLR** (14 to 17-year-olds)
Children's Version (Interview)	Children's Version	Teenagers' Version
	Physical Well-Being	
1 ..... kendimi hasta hissettim.	1 ..... kendimi hasta hissettim.	1 ..... kendimi hasta hissettim.
2 ..... başağrım veya karın ağrım oldu	2 ..... başağrım veya karın ağrım oldu	2 ..... ağrım oldu
	3 ..... yorgun ve bitkindim	3 ..... yorgun ve bitkindim
	4 ..... kendimi güçlü ve enerji dolu hissettim	4 ..... kendimi güçlü ve enerji dolu hissettim
	Emotional Well-Being	
3 .....eğlendim ve çok güldüm	5 .....eğlendim ve çok güldüm	5 .... eğlendim ve çok güldüm
4 .....canım sıkıldı	6 .....canım sıkıldı	6 .... canım sıkıldı.
	7 .....kendimi yalnız hissettim.	7 .... kendimi yalnız hissettim.
	8 .....korktum.	8 .... korktum veya kendime güvenimi kaybettim

Self-Esteem		
5.....kendimle gurur duydum.	9.....kendimle gurur duydum	9.....kendimle gurur duydum
6.....kendimden hoşlandım. (kendimden memnun oldum)	10.....kendimi herşeyin üstünde hissettim.	13.....kendimi herşeyin üstünde hissettim.
	11.....kendimden hoşnutluk duydum	10.....kendimden hoşnutluk duydum
	12.....birçok güzel düşüncem vardı	11.....birçok güzel düşüncem vardı.
Family		
7.....annem babamla aram iyiydi	9.....annem babamla aram iyiydi.	13.....annem babamla aram iyiydi.
8.....evde kendimi iyi hissettim.	13.....evde kendimi iyi hissettim.	14.....evde kendimi iyi hissettim
	14.....evde tartıştık.	15.....evde tartıştık.
	15.....annem babam bazı şeyleri yapmamı engellediler.	16.....annem Babam tarafından kısıtlandığımı hissettim
Friends		
9.....arkadaşlarımla oynadım.	17.....arkadaşlarımla oynadım.	17.....Arkadaşlarımla birlikte bir şeyler yaptık.
10.... arkadaşlarımla iyi geçindim	18.....diğer çocuklar benden hoşlandılar	18.....Arkadaşlarım arasında "başarılıydım"
	19.....arkadaşlarımla iyi geçiniyordum	19.....Arkadaşlarımla iyi geçiniyordum
	20.....kendimi diğer çocuklardan farklı veya önemsiz hissettim	
Everyday Functioning (School or Nursery School/Kindergarten)		
11.....ana okulu/kreşte verilen ödevleri görevleri yapabiliyordum	21.....okul ödevimi yapmak kolaydı	21.....okuldaki ödevleri başarıyla yaptım
12.....anaokulu/kreşten hoşlandım	22.....derslerden hoşlandıım	22.....ders ilgimi çekti
	23.....önümüzdeki haftaların gelmesini dört gözle bekledim	23.....okulda bundan sonra geçireceğim günler beni kaygılandırıyor (endişelendiriyor).
	24.....zatıf notlar almaktan korktum	24.....zayıf not almaktan korktum
"Disease" Module		
13. Şu anda hastanede mi kalıyorsunuz veya uzun süreli bir hastalığınız var mı? (Filtre sorusu)	25. Şu anda hastanede mi kalıyorsunuz veya uzun süreli bir hastalığınız var mı (Filtre sorusu)	25. Şu anda hastanede mi kalıyorsunuz veya uzun süreli bir hastalığınız var mı (Filtre sorusu)
14.....hastalığımın kötüleşmesinden korktum	26.....hastalığımın kötüleşmesinden korktum	26.... hastalığımın kötüleşmesinden korktum
15.....hastalığım nedeniyle üzüldüm	27.....hastalığım nedeniyle üzüldüm	27.... hastalığım nedeniyle üzüldüm
16.....hastalığımla çok iyi başa çıkabildim.	28.....hastalığımla çok iyi başa çıkabildim	28.... hastalığımla çok iyi başa çıkabildim
17.....annem babam hastalığım nedeniyle bana bebek gibi baktılar	29.....annem babam bana hastalığım nedeniyle bebekmişim gibi davrandı.	29.....annem babam bana hastalığım nedeniyle bebekmişim gibi davrandı.
18.....diğer insanların hastalığımı fark etmelerinden çekindim.	30.....diğer insanların hastalığımı fark etmelerinden çekindim.	30.....diğer insanların hastalığımı fark etmelerinden çekindim.
19.....hastalığım nedeniyle anaokulu/kreşte bazı şeyleri kaçırdım	31.....hastalığın nedeniyle okulda bazı şeyleri kaçırdım	31.....hastalığım nedeniyle okulda bazı şeyleri kaçırdım

1.1.3.2 Parents' versions

Kiddy-KINDLR (3 to 6-year-olds)	**KINDLR** (7 to 17-year-olds)
Parents' Version	Parents' Version
Physical Well-Being	
1 ....çocuğum kendini hasta hissetti	1 .... çocuğum kendini hasta hissetti
2 .... çocuğumun baş agrısı veya karın ağrısı oldu	2 .... çocuğumun baş agrısı veya karın ağrısı oldu
3 ....çocuğum yorgun ve bitkindi	3 .... çocuğum yorgun ve bitkindi.
4 ....çocuğum kendini güçlü ve enerji dolu hissetti	4 .... çocuğum kendini güçlü ve enerji dolu hissetti
Emotional Well-Being	
5 ....çocuğum eğlendi ve çok güldü	5 ....çocuğum eğlendi ve çok güldü
6 ....çocuğumun canı herhangi bir şey yapmak istemedi	6 ....çocuğum kendini yalnız hissetti
7 .... çocuğum kendini yalnız hissetti	9 ....çocuğumun canı herhangi bir şey yapmak istemedi
8 ....çocuğum korku duydu veya kendinden emin olamadı	10 ..çocuğum korku duydu veya kendinden emin olamadı
Self-Esteem	
9 .....çocuğum kendisiyle gurur duydu	9 ......çocuğum kendisiyle gurur duydu
10 ... çocuğum kendini herşeyin üstünde hissetti.	10 ....çocuğum kendini herşeyin üstünde hissetti.
11 ... çocuğum kendinden memnundu.	11 ....çocuğum kendinden memnundu
12 ... çocuğumun birçok güzel düşüncesi vardı.	12 ....çocuğumun birçok güzel düşüncesi vardı.
Family	
13 ....çocuğum anne babası olarak bizimle iyi geçindi	13 .... çocuğum anne babası olarak bizimle iyi anlaştı
14 .... çocuğum evde kendini iyi hissetti	14 .... çocuğum evde kendini iyi hissetti.
15 .... evde çocuğumla tartıştık	15 .... evde çocuğumla tartıştık
16 .... çocuğum benim kendisine hükmettiğimi düşündü.	16 .... çocuğum benim kendisine hükmettiğimi düşündü
Friends	
17 .....çocuğum arkadaşlarıyla oynadı	17 .....çocuğum arkadaşlarıyla birlikte bir şeyler yaptı
18 .....başka çocuklar çocuğumdan hoşlandılar.	18 .....başka çocuklar çocuğumdan hoşlandılar.
19 .....çocuğum arkadaşlarıyla iyi geçindi	19 .....çocuğum arkadaşlarıyla iyi geçindi
20 .....çocuğum kendini diğer çocuklardan farklı hissetti.	20 .....çocuğum kendini diğer çocuklardan farklı hissetti
Everyday Functioning (School or Nursery School/Kindergarten)	
21 .....çocuğum anaokulu/kreşte verilen ödevlerle başa çıkabildi.	21 .....çocuğum okulda verilen ödevlerle başa çıkabildi.
22 .....çocuğum anaokulu/kreşten memnundu.	22 .....çocuğum okuldaki derslerden hoşnuttu.
23 .....çocuğum anaokulunu/kreşine gitmeyi dört gözle bekledi.	23 .....çocuğum geleceği hakkında ekaygılıydı
24 .....Çocuğum basit görevleri veya ev ödevlerini yaparken birçok hata yaptı.	24 .....çocuğum okulda kötü not almaktan korktu
"Disease" Module	
47..... Çocuğunuz şu anda hastanede mi kalıyor veya uzun süreli bir hastalığı var mı? (Filtre sorusu)	25..... Çocuğunuz şu anda hastanede mi kalıyor veya uzun süreli bir hastalığı var mı? (Filtre sorusu)
48..... çocuğum hep hastalığının kötüleşmesinden korktu	26..... çocuğum hep hastalığının kötüleşmesinden korktu
49..... çocuğum hastalığı nedeniyle üzgündü	27..... çocuğum hastalığı nedeniyle üzgündü
50..... çocuğum hastalığıyla çok iyi başa çıkabildi	28 ..... çocuğum hastalığıyla çok iyi başa çıkabildi
51..... çocuğumuza hastalığı nedeniyle küçük bir çocuk (bebekmiş) gibi daha davrandık,	29 ..... çocuğumuza hastalığı nedeniyle küçük bir çocuk (bebekmiş) gibi daha davrandık
52..... çocuğum diğer insanların hastalığını fark etmelerinden çekindi	30 ..... çocuğum diğer insanların hastalığını fark etmelerinden çekindi
53..... çocuğum hastalığı nedeniyle anaokulu/kreşte bazı şeyleri kaçırdı	31 ..... çocuğum hastalığı nedeniyle okulda bazı şeyleri kaçırdı

Kiddy-KINDLR (3 to 6-year-olds)
Parents' Version
Additional Items "Kiddy Parents"
25..... çocuğum içine kapanık ve çok mızmızdı.
26..... çocuğumun iştahı iyiydi
27..... çocuğuma sabır ve anlayış gösterebildi.
28..... çocuğum kendini baskı altında hissetti
29..... çocuğum derin derin uyudu
30..... çocuğum ortalıkta sıçrıyordu ve çok hareketliydi
31..... birden çocuğumun gözünden yaşlar boşandı.
32..... çocuğum neşeli ve iyi bir ruh hali içindeydi.
33..... çocuğum uyanık ve ilgisini çok iyi toparlayabilecek durumdaydı
34..... çocuğumun ilgisini çabuk kaybederdi ve dalgındı
35..... çocuğum diğer çocuklarla birlikte olmaktan hoşlandı
36..... çocuğumu azarlamak zorunda kaldım.
37..... çocuğumu övdüm.
38..... çocuğumun öğretmenlerle ile veya anaokulu bakıcılarıyla veya diğer çocuk bakıcılarıyla sorunları vardı
39..... çocuğum sinirli ve yerinde duramayan bir çocuktu.
40..... çocuğum canlı ve enerji doluydu
41..... çocuğum ağrıdan şikayet etti
42..... çocuğum girişken ve dışa dönüktü
43..... çocuğum yapmaya kalkıştığı her şeyi başarmıştı.
44..... çocuğum çok çabuk mutsuz oldu.
45..... çocuğum içli içli ağladı
46..... çocuğumun çabucak huyu değişti.

1.2. Calculation of Sub-Scale Scores

1.2.1. Kid-KINDL^R and Kiddo-KINDL^R

When analysing the KINDL^R questionnaire on the quality of life of children and adolescents in the age range of 7 to 17-year-olds, the following six sub-scale scores can be calculated:

1. Physical Well-being (Items 1L, 2L, 3L, 4)
2. Emotional Well-being (Items 5, 6L, 7L, 8L)
3. Self-esteem (Items 9, 10, 11, 12)
4. Family (Items 13, 14, 15L, 16L)
5. Friends (Items 17, 18, 19, 20L)
6. School (Items 21, 22, 23L, 24L)

A Total Score is formed for all the items. Finally, if necessary an additional sub-scale can be calculated using the six questions in the "Disease" module:

7. Disease (Items 26L, 27L, 28, 29L, 30L, 31L)

The values are as follows:

1 = never

2 = rarely

3 = sometimes

4 = often

5 = all the time

Missing value = "blank"

Important! The items marked with a L have to be reversed, i.e. 1=5, 2=4, 3=3, 4=2, 5=1. Response value 5 ("all the time") must be the positive end of the item

1.2.1.1 Formulae and examples for calculating sub-scale sum scores

Sum score = Sum of sub-scale items

Sub-scale score = Sum of sub -scale items/ Number of sub -scale items

Example: Physical well-being sub-scale score =Sum of Items 1, 2, 3, 4/4

Total sub-scale score = Sum of all items Sub-scales / Number of all items

Transformed to 100 = ((Sub-scale score -lowest possible score)/ Possible range of raw score)x100

1.2.2 Kiddy-KINDL^R

The calculation of sub-scale scores for the parents' version of the Kiddy KINDL^R is essentially the same as described above for the other KINDL^R versions. However, the 22 additional items (Items 25 to 46) form a separate sub-scale known as "Kiddy Parents". Here the following items need to be reversed: 25, 28, 31, 34, 36, 38, 39, 41, 44, 45, 46, 48, 49, 51, 52, 53.

In the self-assessment version of the Kiddy interview, only the total score is calculated, and where necessary the additional sub-scale "Disease". The values for the children's version are as follows:

1 = never

2 = sometimes

3 = very often

Table S1. Normative data and discriminative properties of KINDL^R

	Children (7 -13 years old) n =918				Adolescents (14 -17 years old) n=583			
	Girl		Boy		Girl		Boy	
	mean	s.d.	mean	s.d.	mean	s.d.	mean	s.d.
KINDL^R - Total Score -100	76.83	8.63	76.67	8.66	70.78	10.01	73.54	8.83
KINDL^R – Physical Well-being-100	74.43	14.19	76.68	13.03	68.24	17.38	77.18	13.07
KINDL^R – Emotional Well-being -100	83.11	11.33	82.89	10.67	79.41	12.89	79.49	11.80
KINDL^R – Self-Esteem -100	66.68	17.83	66.52	18.95	58.14	19.06	63.27	19.34
KINDL^R– Family -100	84.40	12.85	83.58	13.14	75.51	17.68	79.56	17.05
KINDL^R – Friends -100	78.10	13.78	78.21	12.78	78.06	13.47	78.43	11.96
KINDL^R - School -100	74.10	12.29	72.35	12.88	65.19	13.21	63.58	14.04
KINDL^R – Disease -100	60.56	15.25	64.17	13.75	60.10	14.80	64.91	12.90

1.3. Interpretation and Reference Values

The scores achieved on the individual KINDL^R sub-scales and the KINDL^R total score represent a quantification of the subject's health-related quality of life from the respondent's point of view. There are three ways of interpreting these scores: first of all, the values within the individual sub-scales can be studied directly. The distance from the possible limits (maximum and minimum achievable values) can give a first indication of a respondent's self-assessment. The second means of interpretation consists in comparing the sub-scale scores of individuals. In a third possible means of interpretation, changes in the patient's clinical condition can be related to changes in his or her self-reported health status based on clinical measurements and quality of life data collected at the same time. Until the data from a standard sample is available for the KINDL^R questionnaire, the results of a large sample of Hamburg school children (n=1501) can be used as a preliminary reference for healthy children **(Table S1).** For the following reference values of the sub-scales transformed to a base of 100, the items missing from the short version have been estimated using regression analysis. The scores for the "Disease" module are based on a sample of chronically ill children. Here again, the scale has been transformed to a range of 0 to 100.

2. Short Form Health Survey (SF-36) questionnaire

2.1 SF-36 questionnaire items

1. In general, would you say your health is:

(5) Excellent

(4) Very good

(3) Good

(2) Fair

(1) Poor

2. **Compared to one year ago,** how would you rate your health in general **now**?

(5) Much better now than one year ago

(4) Somewhat better now than one year ago

(3) About the same

(2) Somewhat worse now than one year ago

(1) Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	(1)	(2)	(3)
b. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	(1)	(2)	(3)
c. Lifting or carrying groceries	(1)	(2)	(3)
d. Climbing **several** flights of stairs	(1)	(2)	(3)
e. Climbing **one** flight of stairs	(1)	(2)	(3)
f. Bending, kneeling, or stooping	(1)	(2)	(3)

g. Walking **more than a mile**	(1)	(2)	(3)
h. Walking **several blocks**	(1)	(2)	(3)
i. Walking **one block**	(1)	(2)	(3)
j. Bathing or dressing yourself	(1)	(2)	(3)

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
a. Cut down the **amount of time** you spent on work or other activities	(1)	(2)
b. **Accomplished less** than you would like	(1)	(2)
c. Were limited in the **kind** of work or other activities	(1)	(2)
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	(1)	(2)

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
a. Cut down the amount of time you spent on work or other activities	(1)	(2)
b. Accomplished less than you would like	(1)	(2)
c. Didn't do work or other activities as carefully as usual	(1)	(2)

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(5) Not at all
(4) Slightly
(3) Moderately
(2) Quite a bit
(1) Extremely

7. How much **bodily** pain have you had during the **past 4 weeks**?:

(5) None
(4) Mild
(3) Moderate
(2) Severe
(1) Very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(5) Not at all
(4) A little bit
(3) Moderately
(2) Quite a bit
(1) Extremely

9. How TRUE or FALSE is **each** of the following statements for you

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	(1)	(2)	(3)	(4)	(5)
b. I am as healthy as anybody I know	(5)	(4)	(3)	(2)	(1)
c. I expect my health to get worse	(1)	(2)	(3)	(4)	(5)
d. My health is excellent	(5)	(4)	(3)	(2)	(1)

10. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	(6)	(5)	(4)	(3)	(2)	(1)
b. Have you been a very nervous person?	(1)	(2)	(3)	(4)	(5)	(6)
c. Have you felt so down in the dumps that nothing could cheer you up?	(1)	(2)	(3)	(4)	(5)	(6)
d. Have you felt calm and peaceful?	(6)	(5)	(4)	(3)	(2)	(1)
e. Did you have a lot of energy?	(6)	(5)	(4)	(3)	(2)	(1)
f. Have you been a happy person?	(6)	(5)	(4)	(3)	(2)	(1)
g. Have you felt downhearted and blue?	(1)	(2)	(3)	(4)	(5)	(6)
h. Did you feel worn out?	(1)	(2)	(3)	(4)	(5)	(6)
i. Did you feel tired?	(1)	(2)	(3)	(4)	(5)	(6)
j. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?	(1)	(2)	(3)	(4)	(5)	(6)

2.2 Validated Turkish SF-36 questionnaire items

1. Genel olarak sağlığınızı nasıl değerlendirirsiniz?

(5) Mükemmel
(4) Çok iyi
(3) İyi
(2) Fena değil
(1) Kötü

2. Geçen seneyle karşılaştırıldığında şimdi sağlığınızı nasıl değerlendirirsiniz?

(5) Bir yıl öncesine göre çok daha iyi
(4) Bir yıl öncesine göre daha iyi
(3) Hemen hemen aynı
(2) Bir yıl öncesine göre daha kötü
(1) Bir yıl öncesinden çok daha kötü

3. Aşağıdakiler normal olarak gün içerisinde yapıyor olabileceğiniz bazı faaliyetlerdir. Şu sıralarda sağlığınız sizi şu faaliyetler bakımından kısıtlıyor mu? Kısıtlıyorsa ne kadar?

	Evet, oldukça kısıtlıyor	Evet, biraz kısıtlıyor	Hayır, hiç kısıtlamıyor
a. Kuvvet gerektiren faaliyetler örneğin ağır eşyalar kaldırma, futbol gibi sporlarla uğraşmak	(1)	(2)	(3)
b. Orta zorlukta faaliyetler, örneğin masa kaldırmak, süpürmek, yürüyüş gibi hafif spor yapmak	(1)	(2)	(3)
c. Çarşı, pazar torbalarını taşımak	(1)	(2)	(3)
d. Birkaç kat merdiven çıkma	(1)	(2)	(3)
e. Bir kat merdiven çıkmak	(1)	(2)	(3)
f. Eğilmek, diz çökmek, yerden bir şey almak	(1)	(2)	(3)
g. Bir kilometreden fazla yürümek	(1)	(2)	(3)
h. Birkaç yüz metre yürümek	(1)	(2)	(3)
i. Yüz metre yürümek	(1)	(2)	(3)
j. Yıkanmak yada giyinmek	(1)	(2)	(3)

4. Geçtiğimiz bir ay (4 hafta) içerisinde işinizde veya diğer günlük faaliyetlerinizde bedensel sağlığınız nedeniyle aşağıdaki sorunların herhangi biriyle karşılaştınız mı?

	Evet	Hayır
a. İş ya da iş dışı uğraşlarınıza verdiğiniz zamanı kısmak zorunda kalmak?	(1)	(2)
b. Yapmak istediğinizden daha azını yapabilmek? (bitmeyen proje, temizlenmeyen ev…)	(1)	(2)
c. Yapabildiğiniz iş türünde yada diğer faaliyetlerinizde kısıtlanmak?	(1)	(2)
d. İşiniz yada diğer uğraşları yapmakta zorlanmak	(1)	(2)

5. Geçtiğimiz bir ay (4 hafta) içerisinde işinizde veya diğer günlük faaliyetlerinizde duygusal problemleriniz nedeniyle (üzüntülü ya da kaygılı olmak gibi) aşağıdaki sorunların herhangi biriyle karşılaştınız mı?

	Evet	Hayır
a. İş yada iş dışı uğraşlarınıza verdiğiniz zamanı kısmak zorunda kalmak?	(1)	(2)
b. Yapmak istediğinizden daha azını yapabilmek? (bitmeyen proje, temizlenmeyen ev…)	(1)	(2)
c. İş yada diğer uğraşları her zamanki gibi dikkatlice yapamamak?	(1)	(2)

6. Son bir ay (4 hafta) içerisinde bedensel sağlığınız veya duygusal problemleriniz, aileniz, arkadaşlarınız, komşularınızla ya da diğer gruplarla olan normal olarak yaptığınız sosyal faaliyetlere ne kadar engel oldu? Birini işaretleyin:

(5) Hiç
(4) Biraz
(3) Orta derecede
(2) Epeyce
(1) Çok fazla

7. Geçtiğimiz bir ay (4 hafta) içerisinde ne kadar bedensel ağrınız oldu? Birini işaretleyin:

(5) Hiç
(4) Çok hafif
(3) Hafif
(2) Aşırı derecede
(1) Çok aşırı derecede

8. Son bir ay (4 hafta), ağrı normal işinize (ev dışında ve ev işi) ne kadar engel oldu? Birini işaretleyin:

(5) Hiç olmadı
(4) Biraz
(3) Orta derece
(2) Epeyce
(1) Çok fazla

9. Aşağıdaki sorulardan size en uygun olan doğru veya yanlışı seçiniz.

	Kesin doğru	Kısmen doğru	Emin değil	Kısmen yanlış	Kesin yanlış
a. Diğer insanlardan kolay hastalanıyorum	(1)	(2)	(3)	(4)	(5)
b. Bildiğim diğer insanlar kadar sağlıklıyım	(5)	(4)	(3)	(2)	(1)
c. Sağlığımın kötüye gideceğini bekliyorum	(1)	(2)	(3)	(4)	(5)
d. Sağlığım mükemmel	(5)	(4)	(3)	(2)	(1)

10. Aşağıdaki sorular geçtiğimiz bir ay (4 hafta) içerisinde kendinizi nasıl hissettiğinizle ve işlerin sizin için nasıl gittiğiyle ilgilidir. Lütfen her soru için nasıl hissettiğinize en yakın olan cevabı verin. Geçtiğimiz 4 hafta içindeki sürenin ne kadarı

	Her zaman	Çoğu zaman	Epeyce	Arada sırada	Çok ender	Hiçbir zaman
a. Kendinizi hayat dolu hissettiniz?	(6)	(5)	(4)	(3)	(2)	(1)
b. Çok sinirli bir kişi oldunuz?	(1)	(2)	(3)	(4)	(5)	(6)
c. Hiçbir şeyin sizi neşelendiremeyeceği kadar moraliniz bozuk ve kötü hissettiniz?	(1)	(2)	(3)	(4)	(5)	(6)
d. Sakin ve huzurlu hissettiniz?	(6)	(5)	(4)	(3)	(2)	(1)
e. Çok enerjiniz oldu?	(6)	(5)	(4)	(3)	(2)	(1)
f. Mutsuz ve kederli oldunuz?	(1)	(2)	(3)	(4)	(5)	(6)
g. Yıpranmış, tükenmiş hissettiniz mi?	(1)	(2)	(3)	(4)	(5)	(6)
h. Kendinizi bitkin hissettiniz?	(1)	(2)	(3)	(4)	(5)	(6)
i. Yorgun hissettiniz?	(1)	(2)	(3)	(4)	(5)	(6)
j. Sağlığınız sosyal aktivitelerinizi sınırladı mı? (arkadaşlarınızı yakın arkadaşlarınızı ziyaret etmek gibi)	(1)	(2)	(3)	(4)	(5)	(6)

2.2. Scoring Rules SF-36 Health Survey

Scoring the 36-Item Health Survey is a two-step process. First, precoded numeric values are recoded per the scoring key given in **Table S1.** Note that all items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range

so that the lowest and highest possible scores are 0 and 100, respectively. Scores represent the percentage of total possible score achieved. In step 2, items in the same scale are averaged together to create the 8 scale scores. **Table S2** lists the items averaged together to create each scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Hence, scale scores represent the average for all items in the scale that the respondent answered.

Table S1. Recoding Items

Item numbers	Response category *	To recoded value of:
1, 2, 6, 7, 8, 9a, 9b, 9c, 9d	5 →	100
	4 →	75
	3 →	50
	2 →	25
	1→	0
3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	3 →	100
	2 →	50
	1 →	0
4a, 4b, 4c, 4d, 5a, 5b, 5c	2 →	100
	1 →	0
10a, 10b, 10c, 10d, 10e, 10f, 10g, 10h, 10i,10j	6 →	100
	5 →	80
	4 →	60
	3 →	40
	2 →	20
	1 →	0
* Precoded response choices as printed in the questionnaire		

Table S2. Averaging Items to Form Scales

Scale	Number of items	After recoding per Table 1, average the following items
Physical functioning	10	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j
Role limitations due to physical health	4	4a, 4b, 4c, 4d,
Role limitations due to emotional problems	3	5a, 5b, 5c
Vitality (Energy/ fatigue)	4	10a, 10e, 10g,10i
Emotional well-being	5	10b, 10c, 10d, 10f, 10h
Social functioning	2	6, 10j
Bodily pain	2	7, 8
General health	5	1, 9a, 9b, 9c, 9d

2.3. Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population

Table S3. Mean (SD) scores for eight variables of SF-36 for women and men

Variables (Number)	Women (n = 670) Mean ± SD	Men (n = 609) Mean ± SD
Physical functioning (1279)	80.6 ± 21.7	87.2 ± 17.1
Role limitations due to physical health	82.9 ± 28.6	89.8 ± 19.3
Role limitations due to emotional problems (1279)	89.0 ± 22.5	92.8 ± 15.1
Vitality (Energy/fatigue) (1271)	63.4 ± 13.7	65.7 ± 11.9
Emotional well-being (1271)	70.1 ± 11.4	71.0 ± 10.6
Social functioning (1279)	90.1 ± 12.9	91.7 ± 12.8
Bodily Pain (1279)	81.0 ± 20.2	85.1 ± 16.4
General health (1279)	69.1 ± 16.9	73.6 ± 14.9

3. Treatment Satisfaction Questionnaire for Medication 9 (TSQM-9)

3.1. TSQM-9 items

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are being asked to assess. We are interested in your evaluation of the effectiveness and convenience of the medication over the last two to three weeks, or since you last used it. For each question, please select the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied

❒3 Dissatisfied
❒4 Somewhat Satisfied
❒5 Satisfied
❒6 Very Satisfied
❒7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

❒1 Extremely Dissatisfied
❒2 Very Dissatisfied
❒3 Dissatisfied
❒4 Somewhat Satisfied
❒5 Satisfied
❒6 Very Satisfied
❒7 Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?

❒1 Extremely Difficult
❒2 Very Difficult
❒3 Difficult
❒4 Somewhat Easy
❒5 Easy
❒6 Very Easy
❒7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

❒1 Extremely Difficult
❒2 Very Difficult
❒3 Difficult
❒4 Somewhat Easy
❒5 Easy
❒6 Very Easy
❒7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

❒1 Extremely Inconvenient
❒2 Very Inconvenient
❒3 Inconvenient
❒4 Somewhat Convenient
❒5 Convenient
❒6 Very Convenient
❒7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

❒1 Not at All Confident
❒2 A Little Confident
❒3 Somewhat Confident
❒4 Very Confident
❒5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

❒1 Not at All Certain
❒2 A Little Certain
❒3 Somewhat Certain
❒4 Very Certain
❒5 Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

❒1 Extremely Dissatisfied
❒2 Very Dissatisfied
❒3 Dissatisfied
❒4 Somewhat Satisfied
❒5 Satisfied
❒6 Very Satisfied
❒7 Extremely Satisfied

3.2 The validated Turkish version of TSQM-9

Talimatlar: Bu klinik çalışmada kullandığınız ilaç hakkındaki memnuniyet veya memnuniyetsizlik düzeyiniz üzerine düşünmek için lütfen zaman ayırın. Son iki ila üç hafta boyunca veya son kullanımınızdan beri ilacın etkinliği, yan etkileri ve kullanım kolaylığı hakkındaki değerlendirmeniz ile ilgileniyoruz. Her soruda, deneyimlerinize en yakın yanıtın yanına lütfen bir onay işareti koyun.

1. İlacın rahatsızlığınızı önleme veya tedavi etme yetisinden ne ölçüde memnunsunuz veya değilsiniz?

❑1 Hiç Memnun Değilim
❑2 Yoğun Ölçüde Memnun Değilim
❑3 Memnun Değilim
❑4 Biraz Memnunum
❑5 Memnunum
❑6 Çok Memnunum
❑7 Oldukça Memnunum

2. İlacın semptomlarınızı giderme yönteminden ne ölçüde memnunsunuz veya değilsiniz?

❑1 Hiç Memnun Değilim
❑2 Yoğun Ölçüde Memnun Değilim
❑3 Memnun Değilim
❑4 Biraz Memnunum
❑5 Memnunum
❑6 Çok Memnunum
❑7 Oldukça Memnunum

3. İlacın etki göstermeye başlamasına kadar geçen vakitten ne ölçüde memnunsunuz veya değilsiniz?

❑1 Hiç Memnun Değilim
❑2 Yoğun Ölçüde Memnun Değilim
❑3 Memnun Değilim
❑4 Biraz Memnunum
❑5 Memnunum
❑6 Çok Memnunum
❑7 Oldukça Memnunum

4. Şu anki haliyle ilacı kullanmak ne ölçüde kolay veya ne ölçüde zor?

❑1 Oldukça Zor
❑2 Çok Zor
❑3 Zor
❑4 Biraz Kolay
❑5 Kolay
❑6 Çok Kolay
❑7 Oldukça Kolay

5. Her seferinde ilacı ne zaman kullanacağınızı planlamak ne kadar kolay veya zor?

❑1 Oldukça Zor
❑2 Çok Zor
❑3 Zor
❑4 Biraz Kolay
❑5 Kolay
❑6 Çok Kolay
❑7 Oldukça Kolay

6. İlacın talimatlarda belirtildiği üzere kullanımı ne ölçüde kolay veya zor?

❑1 Kullanımı Oldukça Zor
❑2 Kullanımı Çok Zor
❑3 Kullanımı Zor
❑4 Kullanımı Biraz Kolay
❑5 Kullanımı Kolay
❑6 Kullanımı Çok Kolay
❑7 Kullanımı Oldukça Kolay

7. Genelde, bu ilacı kullanmanın sizin için iyi olduğuna ne kadar güveniyorsunuz?

❑1 Pek Güvenmiyorum
❑2 Az Ölçüde Güveniyorum
❑3 Biraz Güveniyorum
❑4 Çok Güveniyorum
❑5 Oldukça Güveniyoru

8. İlacınız hakkındaki iyi noktaların kötü noktalardan ağır geldiğinden ne kadar eminsiniz?

❑1 Pek Emin Değilim
❑2 Az Ölçüde Eminim
❑3 Biraz Eminim
❑4 Çok Eminim
❑5 Oldukça Eminim

9. Bütün noktaları göz önüne alındığında, bu ilaçtan ne ölçüde memnunsunuz veya değilsiniz?

❑1 Hiç Memnun Değilim
❑2 Yoğun Ölçüde Memnun Değilim

☐3 Memnun Değilim
☐4 Biraz Memnunum
☐5 Memnunum
☐6 Çok Memnunum
☐7 Oldukça Memnunum

3.3. Subscales and Scoring

The TSQM-9 examines different aspects of treatment satisfaction and has 9 items in four subscales, including effectiveness (1-3), convenience of use (4-6), and overall satisfaction (7-9). 1-6 and 9th items are scored from 1 (strongly disagree) to 7 (strongly agree), and 7th and 8th items are scored from 1 to 5.

The sum of the scores of each subscale is displayed as a number from 0 to 100. To calculate this, the sum of the scores for each subscale minus the number of items in that subscale is divided by the difference between the maximum and minimum possible scores for that subscale, then multiplied by 100**.**

Subscale score:

(Sum of sub-scale items scores-number of subscale items/(Possible range of raw score))X100

Total Score:

(Sum of all items scores-9 /50) X100