

The Effect of Smartphone-Enabled Patient Education on Adherence to Azathioprine Therapy in Adolescents with Inflammatory Bowel Disease: Interim Analysis of a Multicenter Study

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URL: <https://clinicaltrials.gov/ct2/show/NCT05321485?term=MedicijnWijs&draw=2&rank=1>

ClinicalTrials.gov Identifier: NCT05321485

Word count (excluding title, author, abstract, keywords, references, and figure/table legends): 4668

Number of figures: 1

Number of tables: 4

Conflicts of interest: The author declares no conflicts of interest in relation to the submitted work

Funding: The study was funded by Máxima Medical Center, Veldhoven, the Netherlands

The Effect of Smartphone-Enabled Patient Education on Adherence to Azathioprine Therapy in Adolescents with Inflammatory Bowel Disease: Interim Analysis of a Multicenter Study

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ABSTRACT

Background and Objectives: Approximately 50% of children and only 25 to 35% of adolescents with Inflammatory Bowel Disease (IBD) show adequate medication adherence. Good medication adherence is necessary to lower disease activity and elongate periods of remission. The objective of the study was to assess the effect of the smartphone application *MedicijnWijs* on adherence to azathioprine therapy in IBD patients aged 12 up to and including 17 years old. The effect on knowledge about IBD and the ease of use of *MedicijnWijs* were studied as well.

Methods: A multicenter before-and-after study was conducted in three top clinical hospitals in the Netherlands. The participants used *MedicijnWijs* for six weeks. At the beginning and the end of the study, participants filled in two validated questionnaires: the *Medication Adherence Report Scale-5* (MARS-5), which tested the participants' adherence to azathioprine therapy, and the *Inflammatory Bowel Disease Knowledge Inventory Device 2* (IBD-KID2), which tested the participants' knowledge about IBD. Potential changes in the scores compared to baseline were assessed. The ease of use of *MedicijnWijs* was assessed separately at the end of the six-week period.

Results: An interim analysis of the data of the Máxima Medical Center (MMC) cohort was conducted, since the total dataset was not yet available at the time of analysis due to delays in the other two hospitals. Seven participants were included between March 2022 and April 2022. The geometric mean age was 15.6 years old (*IQR* = 15.0-17.0), four participants (57.0%) were female, two (28.6%) had Ulcerative Colitis (UC), three (42.8%) Crohn's Disease (CD), and two (28.6%) IBD unclassified (IBD-U). Two participants were lost to follow-up. The required sample size for generating a power of 80% was not achieved (only 7 out of 21 participants; 33.3%). A Wilcoxon signed-rank test showed a non-significant difference in the MARS-5 score before (geometric mean = 23.0, *IQR* = 22.5-23.5) and after the use of *MedicijnWijs* (geometric mean = 23.2, *IQR* = 22.5-24.0); $Z = -0.272$, $P = 0.785$. Time since diagnosis was significantly positively correlated with the MARS-5 score at baseline ($r = 0.894$, $P = 0.041$). A Wilcoxon signed-rank test showed a non-significant

difference in the IBD-KID2 score before (geometric mean = 7.9, *IQR* = 6.0-11.0) and after the use of *MedicijnWijs* (geometric mean = 9.2, *IQR* = 6.5-12.5); $Z = -0.730$, $P = 0.465$. No other independent variable was significantly associated with the MARS-5 or IBD-KID2 scores of the participants. Overall, the ease of use of *MedicijnWijs* was rated high.

Conclusions: No hard conclusions can be drawn from the study since most results were not statistically significant. Overall, positive trends were observed in improving adherence to azathioprine therapy and knowledge about IBD. In the remainder of the study, the potential of *MedicijnWijs* will be further investigated in a multicenter setting.

Keywords: Crohn's Disease, Ulcerative Colitis, pediatric gastroenterological disease, education, smartphone application.

What Is Known:

- Good medication adherence is key in achieving lower disease activity and longer periods of remission in patients with Inflammatory Bowel Disease (IBD)
- Written and oral education can be used to increase medication adherence

What Is New:

- In the interim analysis, with too little power, the use of *MedicijnWijs* resulted in non-significant, but overall positive trends in improving adherence to azathioprine therapy and knowledge about IBD
- *MedicijnWijs* is easy to use and contains sufficient information

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Inflammatory bowel disease (IBD) is a chronic disease of the gastrointestinal tract with alternating periods of remission and exacerbation. It mainly comprises of Crohn's Disease (CD) and Ulcerative Colitis (UC). When the distinction between CD or UC cannot (yet) be made, the patient will be diagnosed with IBD unclassified (IBD-U). IBD is diagnosed during childhood or adolescence in 20 to 30% of cases [1-4]. Early-onset IBD is often more extensive, more aggressive, and has a poorer prognosis compared to IBD manifestation in adulthood. Consequently, young IBD patients often experience more symptoms such as abdominal pain, diarrhea, and constipation. Moreover, growth impairment and delay in puberty are common problems in children with IBD [5].

Patients with IBD are often treated with medication indefinitely. Good medication adherence is key in achieving lower disease activity and longer periods of remission [6-8]. However, as with other chronic diseases, medication nonadherence is an existing problem in patients with IBD. Nonadherence is defined as the failure of taking medication as the prescriber has intended [8]. It can either be intentional or unintentional. Reasons for nonadherence can for example be adverse drug effects, negative medication beliefs, or simply ignorance or forgetfulness. Medication adherence rates are especially low in children and adolescents. Approximately 50% of children and only 25 to 35% of adolescents with IBD show adequate medication adherence [6,9]. Kane et al showed that patients with UC who were nonadherent to mesalazine maintenance therapy had more than a fivefold greater risk of relapse than adherent patients [7]. This illustrates the importance of finding ways to improve medication adherence in children and adolescents with IBD.

One way to improve medication adherence is to educate patients on their disease and the medication they are taking. Prior research has shown written and oral education can increase medication adherence by approximately 6 to 25% [8]. Tae et al found that nonadherent IBD patients have significantly less knowledge about their medication than adherent IBD patients [10]. Similarly, Lim et al showed that the number of IBD patients that were aware of the adverse drug effects of their medication was significantly higher in the group with good medication adherence [11]. Furthermore, several other studies have shown that higher patient's knowledge about their chronic disease, such as IBD, is associated with higher medication adherence [12-15].

MedicijnWijs is a smartphone application that is developed by the company *Pharmi* (Eindhoven, the Netherlands) to guide pharmacotherapy in patients suffering from chronic diseases as medication is first

prescribed [16]. Amongst others, *MedicijnWijs* contains a six-week module guiding azathioprine therapy.

In the study, the effect of patient education and guidance through the smartphone application *MedicijnWijs* on adherence to azathioprine therapy in adolescents with IBD was assessed. Secondary objectives were to assess the effect on knowledge about IBD and the ease of use of *MedicijnWijs*.

METHODS

Setting and Study Design

This multicenter before-and-after study was conducted in Máxima Medical Center (MMC) in Veldhoven, Catharina Hospital in Eindhoven, and Zuyderland Medical Center in Sittard-Geleen/Heerlen, the Netherlands. It started in March 2022 and it is still ongoing.

Study Population

Adolescents aged 12 up to and including 17 years old were enrolled. All participants were previously diagnosed with IBD (CD, UC, or IBD-U) and were already being treated with azathioprine in one of the participating top clinical hospitals. Eligible participants were identified by their own treating pediatric gastroenterologists. The participants served as their own control. The outcome measures from baseline were compared to those from the end of the study within the same participant.

Intervention

The participants used the smartphone application *MedicijnWijs* for six weeks. The application contains information about azathioprine as well as general information about IBD, specified to disease modality (CD or UC). Contact details of the patient's pharmacy were listed and push notifications were added to remind the patients to take their medication. Moreover, at the start of weeks two, four, and six, questions were asked about the severity of some of the patient's symptoms (i.e. stomach aches and stool frequency in the past 24 hours). These questions were answered using visual analogue scales. The answers were tracked in graphs, so the patient and their pediatric gastroenterologist can track the symptoms in time.

At the beginning of the six-week guidance, two questionnaires that were translated to and validated in Dutch were filled in: the *Medication Adherence Report Scale-5* (MARS-5) [Supplemental Content 1] and the *Inflammatory Bowel Disease Knowledge Inventory Device 2* (IBD-KID2) [Supplemental Content 2].

The MARS-5 is a questionnaire comprising of five statements about medication adherence [17,18]. For each statement, there are five possible answers: 'always' (one point), 'often' (two points), 'sometimes' (three points), 'rarely' (four points), and 'never' (five points). The MARS-5 score is calculated by summing the numeric score from each statement, so the score can range from 5 to 25 points. The higher the score, the better the adherence to azathioprine therapy.

The IBD-KID2 is a questionnaire comprising of 15 questions about IBD in general, nutrition, lifestyle, and treatment of IBD [19]. The questionnaire consists of six multiple choice questions and nine true/false questions. A point is earned for each correct answer with a maximum IBD-KID2 score of 15 points.

After six weeks, the participants filled out the same questionnaires again. Potential changes in the scores compared to baseline were assessed.

During the study, participants used their usual IBD medication. Their treatment did not change due to the study: routine use of comedication, aside from azathioprine, was allowed and participants did not have to change their lifestyle (e.g. nutritional intake or physical activities). The use of the smartphone application *MedicijnWijz* was the only intervention for the participants.

Outcome Measures

The primary outcome change in adherence to azathioprine therapy was measured as the change in MARS-5 score compared to baseline. The secondary outcome change in knowledge about IBD was measured as the change in IBD-KID2 score compared to baseline. The secondary outcome ease of use of *MedicijnWijz* was assessed separately at the end of the six-week period by a number of questions. All data as well as the participant characteristics were collected through *MedicijnWijz*.

Explanatory Variables

Apart from the outcome measures, associations between the MARS-5 or IBD-KID2 score and a number of explanatory variables were examined as well. These variables were age, gender, education level, diagnosis, time since diagnosis, duration of azathioprine use, and use of comedication.

Data Analysis

Sample size calculations were based on the number of participants required to demonstrate a statistically significant change in the secondary outcome knowledge about IBD. A 15 to 20% change compared to baseline was deemed feasible and clinically relevant. Based on a

study of Vernon-Roberts et al, IBD-KID2 scores of children with IBD are often around 8 at baseline [19]. A 15 to 20% change results in a difference in population means of 1.2 to 1.6. For change in knowledge about IBD, the predicted difference in population means was therefore set at the mean of 1.4. A sample size of 19 participants was calculated to be sufficient in demonstrating a significant difference in population means of 1.4. A loss to follow-up of 10% was taken into account, resulting in a requirement of 21 participants.

Descriptive statistics, being frequency counts, percentages, geometric means (which are more accurate than medians with smaller sample sizes) with interquartile ranges (*IQRs*), and ranges (minimum and maximum) were used to summarize participant characteristics. Participant characteristics that were studied were age, gender, education level, diagnosis, time since diagnosis, duration of azathioprine use, and use of comedication. Means with standard deviations (*SDs*) are more reliable when data is normally distributed, while geometric means with *IQRs* are preferred for data with a skewed distribution. The distribution of data was defined as normal if the skewness and kurtosis parameters were between -1 and +1, and the *P*-value of the Shapiro-Wilk test was higher than 0.05. Histograms and boxplots were also plotted to visually check if data followed a normal distribution.

Given the skewed distribution of the data, the primary outcome change in adherence to azathioprine therapy and the secondary outcome change in knowledge about IBD were statistically analyzed using Wilcoxon signed-rank tests at a 5% significance level. Geometric means with *IQRs* were summarized. The secondary outcome ease of use of *MedicijnWijz* was summarized using descriptive statistics, being frequency counts and percentages.

Associations between MARS-5 or IBD-KID2 score and age, education level, diagnosis, and use of comedication were analyzed using Kruskal-Wallis H tests. In case of a significant Kruskal-Wallis H test, separate Mann-Whitney U tests were performed to locate the difference in the outcomes between the subgroups. Associations between MARS-5 or IBD-KID2 score and gender were analyzed using Mann-Whitney U tests. Associations between MARS-5 or IBD-KID2 score and time since diagnosis, and duration of azathioprine use were analyzed using Spearman's rho correlation. All statistical tests were performed at a 5% significance level. Due to small sample sizes per subgroup in the interim analysis, the assumption of each variable having a normal distribution could not be checked accurately. Therefore, it was assumed that all variables were not normally distributed within the subgroups, hence the choice of these nonparametric statistical tests. For the

calculation of the geometric means it was decided that if any value within a subgroup was either negative or zero, the geometric mean was calculated relative to the total of 100%. This method retained the added value of the geometric means, since if any value within the subgroup would be negative or zero, this would automatically result in a geometric mean of zero as well. *IQRs* could not be given due to the small sample sizes per subgroup. Therefore, ranges were shown instead.

Data were analyzed using *IBM SPSS Statistics, version 22* (Armonk, New York, United States). Extreme values were identified using boxplots. If there was no possible explanation for an extreme value, it was excluded from the statistical analysis. Missing values were handled by contacting the participants.

Ethical Considerations

The study involving human participants was reviewed and declared as not subject to the Medical Research Involving Human Subjects Act by the Medical Review Ethics Committee (MEC) Máxima MC on February 28th, 2022 (MEC number: N22.013). Local research approvals were obtained from each participating hospital. All participants, and if under 16 years old also their parents, provided written informed consent to participate in the study.

RESULTS

Interim Analysis

Obtaining local research approvals from all participating top clinical hospitals took longer than expected. Following this time constraint, this research article serves as an interim analysis of data solely from the MMC cohort. Later on, the results from all three hospitals will be summarized in a final research article.

Participant Characteristics

A total of seven participants from MMC were included in the study between March 2022 and April 2022 [Figure 1]. The geometric mean age was 15.6 years old (*IQR* = 15.0-17.0), four participants (57.0%) were female, two (28.6%) had UC, three (42.8%) CD, and two (28.6%) IBD-U.

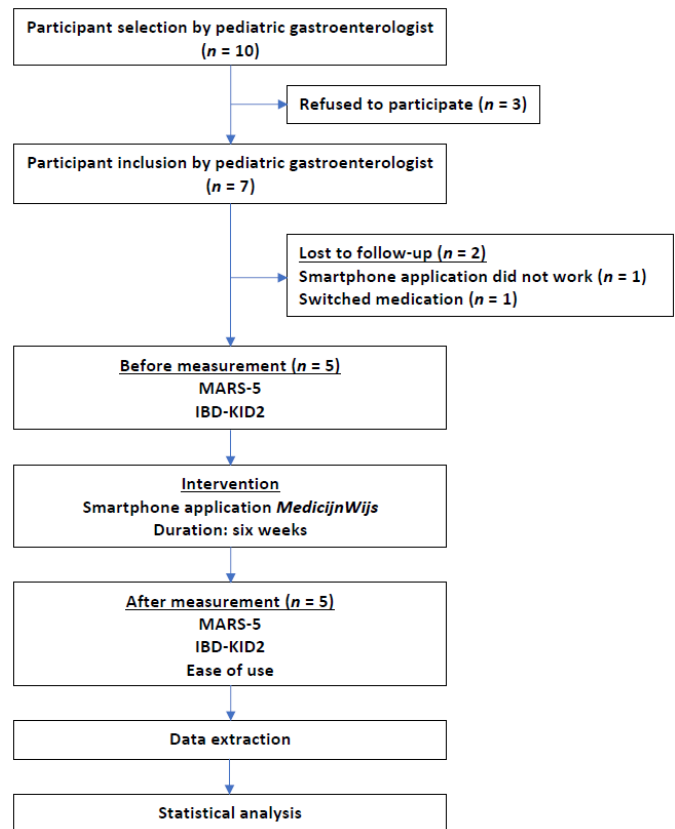


Figure 1: Flowchart study design. The participants were selected by their own treating pediatric gastroenterologist. After inclusion, the participants filled in the MARS-5 and IBD-KID2 questionnaires on day one. After using *MedicijnWijs* for six weeks, they filled in the same questionnaires again as well as some questions on the ease of use of *MedicijnWijs*. Hereafter, data was extracted and statistically analyzed.

The required sample size for generating a power of 80% was not achieved (only 7 out of 21 participants; 33.3%). One of the participants could not get the application to function on their phone and was therefore immediately lost to follow-up. Another patient switched medication and stopped using azathioprine during the first week of the study. Hence, two participants were lost to follow-up. The remaining five participants used *MedicijnWijs* for the complete duration of the study (i.e. six weeks). Age, time since diagnosis, and duration of azathioprine use showed a skewed distribution within the total study population. However, there was a roughly equal distribution of gender, education level, diagnosis, and use of comedication. *Table 1* summarizes the participants' demographic data.

Table 1: Participant characteristics.

Variables	Total (n = 5)	Ulcerative Colitis (n = 2, 40%)	Crohn's Disease (n = 1, 20%)	Inflammatory Bowel Disease Unclassified (n = 2, 40%)
<i>Age (years)</i>				
Geometric mean (IQR)	16.2 (15.5-17.0)	16.5	15.0	16.5
Range	15-17	16-17	15-15	16-17
<i>Gender (n (%))</i>				
Male	2 (40)	1 (50)	1 (100)	-
Female	3 (60)	1 (50)	-	2 (100)
<i>Education level (n (%))</i>				
Vmbo	2 (40)	1 (50)	-	1 (50)
Havo	2 (40)	-	1 (100)	1 (50)
Vwo	1 (20)	1 (50)	-	-
<i>Time since diagnosis (months)</i>				
Geometric mean (IQR)	43.8 (28.0-77.5)	25.3	52.0	69.6
Range	16-103	16-40	52-52	47-103
<i>Duration of use of azathioprine (months)</i>				
Geometric mean (IQR)	34.9 (27.0-47.5)	24.7	52.0	40.4
Range	16-52	16-38	52-52	38-43
<i>Use of comedication (n (%))</i>				
Mesalazine	2 (40)	1 (50)	-	1 (50)
Infliximab	2 (40)	1 (50)	-	1 (50)
None	1 (20)	-	1 (100)	-

IQR = interquartile range (which could only be given for the total study population, due to the small sample sizes per subgroup); vmbo = voorbereidend middelbaar beroepsonderwijs or pre-vocational secondary education; havo = hoger algemeen vormend onderwijs or higher general secondary education; vwo = voorbereidend wetenschappelijk onderwijs or pre-university education.

Adherence to Azathioprine Therapy

The MARS-5 score at baseline showed a skewed distribution within the total study population. The overall geometric mean MARS-5 score at baseline was 23.0 (IQR = 22.5-23.5) out of 25. After six weeks of azathioprine guidance through *MedicijnWijs*, the MARS-5 score showed a skewed distribution again. The overall geometric mean MARS-5 score was 23.2 (IQR = 22.5-24.0). The difference in MARS-5 scores was also unevenly distributed within the total study population. The overall geometric mean difference in MARS-5 scores was 0.2 (IQR = -1.0-1.5). The individual MARS-5 scores as well as the difference scores are summarized in *Supplemental Content 3*.

A Wilcoxon signed-rank test at a 5% significance level was conducted to compare the MARS-5 score before and after the use of *MedicijnWijs*. There was a non-significant difference in the MARS-5 score before (geometric mean = 23.0, IQR = 22.5-23.5) and after the use of *MedicijnWijs* (geometric mean = 23.2, IQR = 22.5-24.0); $Z = -0.272$, $P = 0.785$. The Spearman's rho correlation coefficient showed there was a non-

significant negative relationship between the MARS-5 score before and after the use of *MedicijnWijs* ($r = -0.825$, $P = 0.086$).

Time since diagnosis was significantly positively correlated with the MARS-5 score at baseline ($r = 0.894$, $P = 0.041$). A longer time since diagnosis was associated with higher MARS-5 scores at baseline, and thus with higher adherence to azathioprine therapy. This correlation was not seen for the MARS-5 score after six weeks or the difference in MARS-5 scores. No other independent variable that was tested was significantly associated with the MARS-5 scores of the participants [Table 2].

Apart from the MARS-5, there was also a separate question asked after one week of using *MedicijnWijs* about whether the participant had forgotten to take azathioprine in the past week. Three out of five participants (60%) admitted they had forgotten to take azathioprine during that week.

Table 2: Associations between MARS-5 scores and participant characteristics. Only time since diagnosis showed a significant positive correlation with the MARS-5 score at baseline ($r = 0.894$, $P = 0.041$). The other variables were not significantly associated with the MARS-5 scores of the participants.

	Geometric mean MARS-5 score at baseline (range)	Significance (test statistic, P value)	Geometric mean MARS-5 score after six weeks (range)	Significance (test statistic, P value)	Geometric mean difference in MARS-5 scores (range)	Significance (test statistic, P value)
Categorical variables (n)						
<i>Age in years</i>						
15 (1)	23.0 (23-23)	$H(2) = 2.000$, $P = 0.368$	23.0 (23-23)	$H(2) = 3.500$, $P = 0.174$	0.0 (0-0)	$H(2) = 3.316$, $P = 0.191$
16 (2)	22.5 (22-23)		24.0 (24-24)		1.4 (1-2)	
17 (2)	23.5 (23-24)		22.5 (22-23)		-1.0 (-2-0)	
<i>Gender</i>						
Male (2)	22.5 (22-23)	$U = 1.000$, $Z = -1.291$, $P = 0.197$	23.5 (23-24)	$U = 2.000$, $Z = -0.609$, $P = 0.543$	1.0 (0-2)	$U = 1.500$, $Z = -0.889$, $P = 0.374$
Female (3)	23.3 (23-24)		23.0 (22-24)		-0.3 (-2-1)	
<i>Education level</i>						
Vmbo (2)	23.0 (22-24)	$H(2) = 0.000$, $P = 1.000$	23.0 (22-24)	$H(2) = 0.389$, $P = 0.823$	0.0 (-2-2)	$H(2) = 0.158$, $P = 0.924$
Havo (2)	23.0 (23-23)		23.5 (23-24)		0.5 (0-1)	
Vwo (1)	23.0 (23-23)		23.0 (23-23)		0.0 (0-0)	
<i>Diagnosis</i>						
Ulcerative Colitis (2)	22.5 (22-23)	$H(2) = 2.000$, $P = 0.368$	23.5 (23-24)	$H(2) = 0.389$, $P = 0.823$	1.0 (0-2)	$H(2) = 0.789$, $P = 0.674$
Crohn's Disease (1)	23.0 (23-23)		23.0 (23-23)		0.0 (0-0)	
Inflammatory Bowel Disease Unclassified (2)	23.5 (23-24)		23.0 (22-24)		-0.5 (-2-1)	
<i>Use of comedication</i>						
Mesalazine (2)	23.0 (23-23)	$H(2) = 0.000$, $P = 1.000$	23.5 (23-24)	$H(2) = 0.389$, $P = 0.823$	0.5 (0-1)	$H(2) = 0.158$, $P = 0.924$
Infliximab (2)	23.0 (22-24)		23.0 (22-24)		0.0 (-2-2)	
None (1)	23.0 (23-23)		23.0 (23-23)		0.0 (0-0)	
Continuous variables	r value MARS-5 score at baseline	Significance (P value)	r value MARS-5 score after six weeks	Significance (P value)	r value difference in MARS-5 scores	Significance (P value)
<i>Time since diagnosis</i>	0.894	0.041	-0.738	0.155	-0.821	0.089
<i>Duration of azathioprine use</i>	0.344	0.571	-0.135	0.828	-0.289	0.637

Knowledge About IBD

The IBD-KID2 score at baseline showed a skewed distribution within the total study population. The overall geometric mean IBD-KID2 score at baseline was 7.9 ($IQR = 6.0-11.0$) out of 15. After six weeks of azathioprine guidance through *MedicijnWijz*, the IBD-KID2 score was unevenly distributed again. The overall geometric mean IBD-KID2 score was 9.2 ($IQR = 6.5-12.5$). The difference in IBD-KID2 scores also showed a skewed distribution within the total study population. The overall geometric mean difference in IBD-KID2 scores was 1.2 ($IQR = -1.5-4.5$). The individual IBD-KID2 scores as well as the difference scores are summarized in *Supplemental Content 4*. The percentages of correct answers to the questions of the IBD-KID2 before and after the use of *MedicijnWijz* are presented in *Supplemental Content 5*.

A Wilcoxon signed-rank test at a 5% significance level was conducted to compare the IBD-KID2 score before and after the use of *MedicijnWijz*. There was a non-significant difference in the IBD-KID2 score before (geometric mean = 7.9, $IQR = 6.0-11.0$) and after the use of *MedicijnWijz* (geometric mean = 9.2, $IQR = 6.5-12.5$); $Z = -0.730$, $P = 0.465$. The Spearman's rho correlation coefficient showed there was a non-significant positive relationship between the IBD-KID2 score before and after the use of *MedicijnWijz* ($r = 0.632$, $P = 0.252$).

No independent variable that was tested was significantly associated with the IBD-KID2 scores of the participants [*Table 3*].

Table 3: Associations between IBD-KID2 scores and participant characteristics. No variable was significantly associated with the IBD-KID2 scores of the participants.

	Geometric mean IBD-KID2 score at baseline (range)	Significance (test statistic, P value)	Geometric mean IBD-KID2 score after six weeks (range)	Significance (test statistic, P value)	Geometric mean difference in IBD-KID2 scores (range)	Significance (test statistic, P value)
Categorical variables (n)						
<i>Age in years</i>						
15 (1)	4.0 (4-4)	$H(2) = 2.222, P = 0.329$	10.0 (10-10)	$H(2) = 0.400, P = 0.819$	6.0 (6-6)	$H(2) = 2.400, P = 0.301$
16 (2)	9.4 (8-11)		9.9 (7-14)		1.0 (-1-3)	
17 (2)	9.4 (8-11)		8.1 (6-11)		-1.0 (-2-0)	
<i>Gender</i>						
Male (2)	5.7 (4-8)	$U = 0.500, Z = -1.521, P = 0.128$	8.4 (7-10)	$U = 2.000, Z = -0.577, P = 0.564$	2.4 (-1-6)	$U = 2.000, Z = -0.577, P = 0.564$
Female (3)	9.9 (8-11)		9.7 (6-14)		0.3 (-2-3)	
<i>Education level</i>						
Vmbo (2)	8.0 (8-8)	$H(2) = 1.278, P = 0.528$	6.5 (6-7)	$H(2) = 3.000, P = 0.223$	-1.5 (-2- -1)	$H(2) = 3.600, P = 0.165$
Havo (2)	6.6 (4-11)		11.8 (10-14)		4.2 (3-6)	
Vwo (1)	11.0 (11-11)		11.0 (11-11)		0.0 (0-0)	
<i>Diagnosis</i>						
Ulcerative Colitis (2)	9.4 (8-11)	$H(2) = 2.222, P = 0.329$	8.8 (7-11)	$H(2) = 0.000, P = 1.000$	-0.5 (-1-0)	$H(2) = 2.000, P = 0.368$
Crohn's Disease (1)	4.0 (4-4)		10.0 (10-10)		6.0 (6-6)	
Inflammatory Bowel Disease Unclassified (2)	9.4 (8-11)		9.2 (6-14)		0.5 (-2-3)	
<i>Use of comedication</i>						
Mesalazine (2)	11.0 (11-11)	$H(2) = 4.000, P = 0.135$	12.4 (11-14)	$H(2) = 3.600, P = 0.165$	1.5 (0-3)	$H(2) = 3.600, P = 0.165$
Infliximab (2)	8.0 (8-8)		6.5 (6-7)		-1.5 (-2- -1)	
None (1)	4.0 (4-4)		10.0 (10-10)		6.0 (6-6)	
Continuous variables						
	<i>r value IBD-KID2 score at baseline</i>	Significance (P value)	<i>r value IBD-KID2 score after six weeks</i>	Significance (P value)	<i>r value difference in IBD-KID2 scores</i>	Significance (P value)
<i>Time since diagnosis</i>	-0.369	0.541	-0.300	0.624	0.000	1.000
<i>Duration of azathioprine use</i>	-0.216	0.727	0.462	0.434	0.821	0.089

Ease of Use of MedicijnWijs

The ease of use of *MedicijnWijs* was assessed by a number of questions. Overall, the ease of use was rated high, though one participant could not get the application to function on their phone. Most participants found the information in the application sufficient and useful. 80% of the participants would recommend *MedicijnWijs* to others, though only 40% said the application helped with their everyday medication use. The results of the assessment of the ease of use of *MedicijnWijs* are depicted in Table 4.

Table 4: Results of the assessment of the ease of use of MedicijnWijs. The ease of use of *MedicijnWijs* was rated high, though the application only helped 40% of participants with their everyday medication use.

Questions	Yes	No
Was there enough information?	5 (100)	-
Is <i>MedicijnWijs</i> easy to use?	5 (100)	-
Was the information useful?	4 (80)	1 (20)
Does <i>MedicijnWijs</i> help with your everyday medication use?	2 (40)	3 (60)
Would you recommend <i>MedicijnWijs</i> to others?	4 (80)	1 (20)

Presented as n (%).

DISCUSSION

Based on literature, MARS-5 scores of IBD patients are often around 22 to 23 at baseline [17,20]. Indeed, the MARS-5 scores of the participants of the study were in

the upper range of the scale (geometric mean baseline value of 23.0 (IQR = 22.5-23.5) out of 25). This is conflicting, since medication adherence was expected to be low in adolescents with IBD based on the results of earlier studies [6,9]. In *MedicijnWijs*, apart from the MARS-5, there was also a separate question asked after one week of using the application about whether the participant had forgotten to take azathioprine in the past week. Three out of five participants (60%) admitted they had forgotten to take azathioprine in the past week. This indicates medication adherence at baseline was not as good as the MARS-5 scores made it seem. A shortcoming of the MARS-5 is the uneven distribution of MARS-5 scores that is often seen, resulting in the questionnaire being insensitive. People often score 20 points or higher. In future research, other questionnaires might be better suitable to demonstrate differences in medication adherence over time. Additionally, medication adherence was only measured subjectively. Therefore, social desirability bias could have occurred. In general, medication adherence is known to be overestimated through self-report. In future studies, adherence to azathioprine therapy could for example be measured by using medicine bottles with chips that measure the number of times the bottle is

opened during the study period or by measuring blood levels of azathioprine.

While adherence to azathioprine therapy improved for some participants, for others it decreased after the use of *MedicijnWijs*. The overall geometric mean difference in MARS-5 scores was positive (geometric mean = 0.2, *IQR* = -1.0-1.5). A definitive conclusion cannot be drawn, since the required sample size for generating a power of 80% was not achieved. As a logical consequence, the Wilcoxon signed-rank test did not result in a significant difference in MARS-5 score after the use of *MedicijnWijs* compared to baseline.

However, time since diagnosis was significantly positively correlated with the MARS-5 score at baseline ($r = 0.894$, $P = 0.041$). A possible explanation for this finding is that patients who have been using any type of IBD medication for a longer period of time might have gotten more used to taking azathioprine as well. Moreover, patients who have been diagnosed with IBD for a longer period of time are often more aware of the health consequences of not taking their medication properly. Therefore, they might be more motivated to take azathioprine as prescribed. Also, patients often experience transient side effects when they first start using azathioprine. In patients with a longer time since diagnosis these side effects might have been reduced. This could have resulted in higher MARS-5 scores in participants with a longer time since diagnosis than in participants who had been diagnosed more recently. However, if those reasons were valid, a positive correlation between the MARS-5 score at baseline and the duration of azathioprine use would be expected as well. Although this could still be the case, the interim analysis with too little power did not demonstrate a statistically significant correlation. After six weeks of using *MedicijnWijs*, the correlation between the MARS-5 score and time since diagnosis was no longer observed, nor was it present for the difference in MARS-5 scores. However, these results were not statistically significant. In the final analysis, when the required power is achieved, this result might still change.

The participants of the study had similar IBD-KID2 scores at baseline as the children with IBD in the study of Vernon-Roberts et al, namely a geometric mean baseline value of 7.9 (*IQR* = 6.0-11.0) in the study compared to a mean of 8.5 ($SD = 2.3$) in theirs [19]. Again, knowledge about IBD increased for some participants after the use of *MedicijnWijs*, while it decreased for others. Possibly, participants guessed the answers to some questions instead of actually consciously answering the questions. This could have resulted in lower IBD-KID2 scores after the intervention compared to baseline. The overall geometric mean

difference in IBD-KID2 scores was 1.2 (*IQR* = -1.5-4.5). The Wilcoxon signed-rank test again did not result in a significant difference in IBD-KID2 score after the use of *MedicijnWijs* compared to baseline.

Time since diagnosis was not associated with higher IBD-KID2 scores, though the opposite was expected because patients with a longer time since diagnosis might have researched more about their disease than patients who were diagnosed more recently. However, the finding is in line with other studies that have also shown that time since diagnosis was not associated with higher knowledge levels about IBD [21-23]. A possible explanation might be that information about the disease and medication is obtained shortly after diagnosis and might be forgotten over time. This implies that patient education should be a continuous practice and important information should be reiterated over the course of the disease.

Furthermore, no other independent variable that was tested in the study was significantly associated with the IBD-KID2 scores of the participants. This corresponds to the findings in other studies using the original IBD-KID, though diagnosis was associated with the IBD-KID score in the original validation study [21,23,24]. In the remainder of this multicenter study, after inclusion of the required sample size according to the power analysis, the associations will be studied on a bigger scale which will possibly lead to statistically significant results.

The ease of use of *MedicijnWijs* was rated high. The information in the application was found to be sufficient and useful. Most participants would recommend *MedicijnWijs* to others, while it only helped 40% of the study participants with their everyday medication use. The three participants who said the application did not help them with their everyday medication use were asked to explain why they felt that way and to propose potential improvements for the application. Two participants indicated that the push notifications to remind them to take their medication disappeared too quickly. They would notice the push notification, but then go on with their everyday activities and forget to take azathioprine anyway. A possible improvement would be to incorporate a calendar function in which boxes could be ticked whenever the participant takes their medication. The push notification should then either remain locked until the box is ticked off or it should be sent out every hour until the box is ticked. This improvement was shared with *Pharmi* (Eindhoven, the Netherlands), so they can improve the application for future users. The third participant indicated that she already did not forget to take azathioprine and

therefore *MedicijnWijs* did not significantly help remind her to take her medication.

Lastly, *MedicijnWijs* did not function on the phone of one of the participants. Therefore, the software of the application should be optimized to ensure this problem will not occur again. Accordingly, this was communicated with *Pharmi* (Eindhoven, the Netherlands).

Strengths and Limitations

An important strength of the study was its design. Confounding bias was minimized since each participant served as their own control. Therefore, the only measurable differences were those in adherence to azathioprine therapy and knowledge about IBD.

The burden associated with participating in the study was low. The time burden was only 0 to 10 minutes per day for six weeks. No physical examinations, blood tests, or other tests were performed apart from routine care of IBD. This resulted in a low amount of loss to follow-up.

Loss to follow-up was also minimized by monitoring whether the participants had filled in both questionnaires at the beginning and the end of their six-week study period. Missing data were tracked by contacting the participants to ensure no data was missing.

Since the study will be a prospective multicenter study performed in three different top clinical hospitals, the generalizability of the findings will be relatively high.

A limitation of the study was that the study population consisted of IBD patients that were already using azathioprine for a longer period of time (geometric mean duration of azathioprine use of 34.9 months ($IQR = 27.0-47.5$)) instead of patients that were just starting with azathioprine therapy. The population of adolescents with IBD that are starting with azathioprine therapy is small. Only 20 weeks were available for this research project at Utrecht University and therefore it was not possible to include enough participants if that inclusion criterion was chosen. However, *MedicijnWijs* is intended for the period after azathioprine is first prescribed. Especially in new users of azathioprine a positive effect of *MedicijnWijs* on both medication adherence and knowledge about IBD is expected. New users learn a lot about their disease and medication during the first few weeks of using azathioprine. Those patients can then for example read about the side effects in the beginning of their treatment and learn that they are often transient. This could improve their adherence to azathioprine therapy. The study population of existing users in the study were already more used to taking azathioprine, possibly resulting in

an underestimation of the effect of *MedicijnWijs* on adherence to azathioprine therapy. The same could be true for knowledge about IBD. The study therefore provides insight into the effect of *MedicijnWijs* on the learning curve of existing users, but the effect on new azathioprine users is expected to be bigger. No significant associations between the study outcomes and time since diagnosis and duration of azathioprine use were found in the interim analysis, except for the positive correlation between the MARS-5 score at baseline and time since diagnosis ($r = 0.894, P = 0.041$). After the required sample size will be achieved, this possibly still changes.

Because the study population consisted of existing azathioprine users, the participants did not appear to be intolerant to azathioprine. Therefore, there is a possibility of selection bias in the study.

Furthermore, no control group was used in the study. Therefore, it cannot be determined whether the participants' adherence to azathioprine therapy and/or knowledge about IBD would have changed without the intervention of the use of *MedicijnWijs*.

Lastly, the secondary outcome change in knowledge about IBD was measured through the IBD-KID2 with multiple choice questions and true/false questions. With those types of questions, the probability of guessing should be taken into account. In the study, it was not corrected for. However, for each question of the IBD-KID2 there was the option to choose the answer 'I don't know'. Due to how often this answer was chosen, it is reasonable to conclude the participants have not guessed the answers to the questions often. However, in future research it might be favorable to use questionnaires with open questions. This way, knowledge gaps are easier to demonstrate and repair.

CONCLUSION

Improving medication adherence as well as knowledge about IBD is important in order to develop self-management skills as adolescents transition from childcare to adult care. Smartphone applications are a great way to make adolescents more aware of their disease. Nowadays, most adolescents carry a smartphone with them which they use frequently throughout the day. With *MedicijnWijs*, they carry information about their disease and medication as well as a reminder to take their medication with them at all times. This makes a smartphone application a particularly suitable way of pharmacotherapy guidance in this age group.

No hard conclusions can be drawn from the interim analysis of the study, since most results were not statistically significant due to not achieving the required sample size. However, there was a significant positive

correlation between time since diagnosis and MARS-5 score at baseline ($r = 0.894$, $P = 0.041$). Moreover, overall positive trends were observed in improving adherence to azathioprine therapy and knowledge about IBD. Therefore, it is cautiously concluded that patient education through *MedicijnWijs* can potentially help young IBD patients in their transition to adult care. The study is being continued in a multicenter setting, hopefully achieving the required sample size and possibly leading to statistically significant findings. With these future results, more can be said about the potential of *MedicijnWijs* in this specific patient group. In the future, the application can also be further optimized to provide even better patient guidance not only in young IBD patients but also in patients of other age groups, and possibly with other diseases as well.

Data Availability Statement

During the study, the software program *ResearchManager* was used to store all research data and protect it from unauthorized access. All data was stored anonymously. A study-specific confidentiality agreement was signed by the researchers to protect the participants' privacy. The raw data of the study will be made available by the authors.

Supplemental Content

Supplemental Content for this article can be found in the appendix. The research protocol is available as well.

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