



Original Article

# Efficacy of Home Telemonitoring versus Conventional Follow-up: A Randomized Controlled Trial among Teenagers with Inflammatory Bowel Disease

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## Abstract

**Background and Aims:** Conventional follow-up of teenagers with inflammatory bowel diseases [IBD] is done during scheduled outpatient visits regardless of how well the patient feels. We designed a telemonitoring strategy for early recognition of flares and compared its efficacy with conventional follow-up.

**Methods:** We used a multicentre randomized trial in patients aged 10–19 years with IBD in clinical remission at baseline. Participants assigned to telemonitoring received automated alerts to complete a symptom score and send a stool sample for measurement of calprotectin. This resulted in an individual prediction for flare with associated treatment advice and test interval. In conventional follow-up the health check interval was left to the physician's discretion. The primary endpoint was cumulative incidence of disease flares. Secondary endpoints were percentage of participants with a positive change in quality-of-life and cost-effectiveness of the intervention.

**Results:** We included 170 participants [84 telemonitoring; 86 conventional follow-up]. At 52 weeks the mean number of face-to-face visits was significantly lower in the telemonitoring group compared to conventional follow-up [3.6 vs 4.3,  $p < 0.001$ ]. The incidence of flares [33 vs 34%,  $p = 0.93$ ] and the proportion of participants reporting positive change in quality-of-life [54 vs 44%,  $p = 0.27$ ] were similar. Mean annual cost-saving was €89 and increased to €360 in those compliant to the protocol.

**Conclusions:** Telemonitoring is as safe as conventional follow-up, and reduces outpatient visits and societal costs. The positive impact on quality-of-life was similar in the two groups. This strategy is attractive for teenagers and families, and health professionals may be interested in using it to keep teenagers who are well out of hospital and ease pressure on overstretched outpatient services.

**Trial registration:** NTR3759 [Netherlands Trial Registry]

**Key Words:** Telemonitoring; e-health; cost-effectiveness

## 1. Introduction

Inflammatory bowel disease [IBD], consisting of Crohn's disease and ulcerative colitis, is a chronic, relapsing disorder of the gastrointestinal tract. Inflammation waxes and wanes over time in a seemingly unpredictable fashion. Treatment is aimed at inducing and maintaining disease remission and at preserving functional status and quality-of-life.<sup>1</sup> Approximately 50% of patients with IBD have a disease course that is typically described by a decline in severity after a fierce onset of symptoms, while the other half experience a deterioration or persistence of chronic symptoms.<sup>2,3</sup>

Follow-up of patients with IBD traditionally consists of regular prescheduled visits regardless of how well the patient feels. Disease flares are most likely to occur at times between scheduled visits.

Twenty per cent of patients with IBD is diagnosed before the age of 20 years,<sup>4,5</sup> and the incidence is increasing.<sup>6</sup> Health professionals confronted with the increased disease burden may be interested in finding ways to ease the pressure on overstretched outpatient clinics with new approaches to monitor disease activity in IBD.

Telephone and Internet technologies are currently widely available to measure disease activity at a distance.<sup>7</sup> Patients can share disease activity information electronically with their care provider and receive feedback between hospital visits. In this way patients could be seen at times of clinical need and specialist services could become more efficient. In adults with IBD, telemonitoring programmes led to earlier recognition of disease flares, better quality-of-life and lower healthcare costs.<sup>7,8</sup> The feasibility of home telemonitoring in teenagers is less well known. Although their cognitive ability and capacity to reason are similar to those of adults, they may have inner conflicts regarding autonomy that can result in poor compliance to the monitoring protocol and more adverse outcomes.<sup>9</sup>

We designed a home telemonitoring strategy for teenagers with IBD to recognize flares at an early stage and compared its efficacy and cost-effectiveness with conventional follow-up.

## 2. Materials and Methods

### 2.1. Study design and conduct

We performed a multicentre, randomized controlled, open label trial with two parallel groups and a follow-up time of 52 weeks. For

allocation concealment, randomization was carried out using a separate list of computer-generated random allocation numbers for each individual participating centre [involving permuted blocks with a ratio of 1:1 allocation]. The study was registered in the Netherlands Trial Registry [NTR3759] before recruitment of the first participant, and the study protocol was published in an open access journal.<sup>10</sup> The trial was conducted according to the principle of the *Declaration of Helsinki* [59<sup>th</sup> version, October 2008] and in accordance with the Dutch Medical Research Involving Human Subjects Act. The Medical Ethical Committee of the University Medical Centre Groningen approved the study protocol [METC 2013/010]. Secondary approval was obtained from all participating centres. All parents or legal guardians and participants aged 12–19 years gave informed consent prior to randomization.

### 2.2. Participants

Patients between 10 and 19 years old with IBD were eligible for inclusion in case of clinical disease remission for at least 3 months before study enrolment. IBD had to be diagnosed according to Revised Porto criteria more than 6 months before enrolment.<sup>11</sup> Participants were required to have access to a telephone, the Internet and an email address, and to have a good knowledge of the Dutch language. We excluded patients who were treated with anti-tumour necrosis factor [TNF] monoclonal antibodies [because of unavoidable frequent contact with healthcare providers], had an ileostomy or ileoanal pouch, or had any other comorbidity requiring frequent hospital visits. Patients were recruited in 11 centres in the Netherlands [six tertiary care hospitals and five large regional general hospitals]. National treatment guidelines<sup>12</sup> provided uniformity in treatment among centres. First choice maintenance therapy in patients with Crohn's disease included a thiopurine or methotrexate. Maintenance therapy in patients with ulcerative colitis was aminosalicylate monotherapy or combination therapy with a thiopurine. Participants with active Crohn's disease during the study period were treated with steroids and gradual dose tapering, or with an exclusive oral polymeric diet for 6 weeks. Participants with active ulcerative colitis during the study period were treated with steroids and aminosalicylate dose escalation. Anti-TNF monoclonal antibodies were indicated after failure of conventional therapy

[step-up], and the moment of initiating anti-TNF therapy was considered a censoring date. Specialists or IBD nurses identified eligible patients in their clinic, and these potential participants received an information pack containing a patient invitation letter, a participant information sheet and consent forms. During the enrolment visit the treating specialist checked whether the patient was in clinical remission.

2.3. Intervention and control

Participants assigned to the experimental arm of the trial received automated email alerts to fill in the symptom score and to send in a stool sample. We used an online disease-specific clinical composite score (Pediatric Ulcerative Colitis Activity Index [PUCAI]<sup>13</sup> and the shortened Pediatric Crohn's Disease Activity Index [shPCDAI]).<sup>14,15</sup> Stool samples were sent to the hospital laboratory of the coordinating study centre and were analysed immediately after arrival with a calprotectin point-of-care test [Quantum Blue® Calprotectin, Bühlmann Laboratories], based on lateral flow technology offering quantitative results within minutes.<sup>16</sup> The results of both the symptom score and the calprotectin stool test were uploaded on the IBD-live website and cumulated in a colour-coded disease flare risk stratification [Figure 1, flarometer] that was visible to the individual participant and the local IBD team. The participant was in the low-risk stratum when the symptom score was below 10 and stool calprotectin was below 250 µg/g. Participants in this low-risk stratum were reassured and advised to retest in 3 months. In the intermediate-risk stratum a shorter test interval was advised before progressing to a decision. Symptomatic participants with calprotectin values above 250 µg/g were considered to have a high risk of disease flare and were advised to contact their specialist. If the participant failed to complete the symptom score, two additional automated reminders were sent in the next 2 weeks. After denial of three email alerts participants were contacted personally by phone or email. Participants in the home telemonitoring arm had health checks in the consultation room of the specialist for adverse effects of the medication every 6 months. Participants assigned to conventional follow-up had regular checks in the consultation room as before the trial regardless

of how well the patient was, and the interval varied according to the physician's discretion. When a participant experienced a flare, rapid access to specialist care was provided for all participants. A health check included, among others, a physician's rating of disease activity and blood sampling.

2.4. Outcomes

The primary outcome was the cumulative incidence of disease flares per group, defined as disease activity necessitating therapy intensification [including steroid therapy, exclusive enteral nutrition, aminosalicylate dose escalation or introduction of anti-TNF antibodies]. Secondary outcomes were the change in quality-of-life and cost-effectiveness measured from a societal perspective. Quality-of-life was measured with the IBD-specific IMPACT-III questionnaire, which comprises 35 questions that were answered with a Likert scale [0–4]. The total score and six subdomain scores [bowel symptoms, systemic symptoms, emotional symptoms, social functioning, body image, treatment/interventions] are presented in a range from 0 to 100, with higher scores representing a higher quality-of-life.<sup>17–19</sup> The cost-effectiveness analysis incorporated all direct and indirect medical and non-medical costs. In addition to our previously published study protocol,<sup>10</sup> we determined predictors of compliance to the home telemonitoring programme, defined as being compliant to 80% or more of the alerts [whether or not after a personal encouragement by email or phone]. Candidate predictors were age, gender, type of disease, time since last relapse, travel distance to the hospital, highest education level of one of the parents and emotional quotient [EQ]. EQ was measured with the Dutch translation of the Bar-On EQ-inventory: Youth Version [Toronto, Canada], which consists of 60 questions subdivided into five domains [intrapersonal, interpersonal, adaptability, stress management and general mood].<sup>20</sup> We used the overall EQ score. Participants with high scores represented effectiveness in dealing with daily demands. Finally, we asked the participants in the home telemonitoring group to give their opinion on participation in telemonitoring. Each item was scored on a five-point Likert scale ranging from strongly agree to strongly disagree.












Probability of disease flare	Symptom score >10	Calprotectin >250 µg/g	Message	Timing next test	No shift to lower stratum?
High			Action required  Contact your doctor	1 month	Consider step-up
Intermediate	 	 	Not sure whether  your IBD is under control	1 month	Consider other diagnostic tests
Low			Your IBD is  under control	3 months	

Figure 1. Flarometer. Algorithm with advice on treatment and the timing of re-measurement.

## 2.5. Sample size

To detect a 15% reduction in the absolute relapse risk after 52 weeks of follow-up with a two-sided significance level of 5% and with 80% power, we calculated that we needed 90 participants per group [taking into account a maximum of 10% loss-to-follow-up].

## 2.6. Randomization and masking

Participants for whom consent or assent was provided were randomly allocated in a 1:1 ratio to one of the two arms of the study according to a computer-generated random sequence stratified by research site and disease type [Crohn's disease vs ulcerative colitis], and using blocks of variable size. The allocation sequence was generated by the biostatistics unit of the University Medical Centre Groningen, and was not available to any member of the research team. Allocation concealment was ensured, as the study website [https://www.ibd-live.nl] did not release the randomization code until the participant had been recruited into the trial. The nature of the intervention did not allow blinding of participants, care providers or outcome assessors.

## 2.7. Statistical analysis

Analysis was conducted according to CONSORT guidelines, following an analysis plan agreed in advance by the independent Data Safety Monitoring Board. We used descriptive statistics to compare baseline characteristics of trial participants by allocated arm. The primary analyses were conducted according to intention-to-treat, meaning that all participants recruited into the study were analysed within the group [home telemonitoring or conventional follow-up] to which they were randomized, irrespective of what care they actually received. Secondary analyses were conducted on a per-protocol base. These analyses were restricted to those participants who were compliant to the study protocol. Participants in the home telemonitoring group were considered compliant when they had replied to 80% or more of the alerts [whether or not after a personal encouragement by phone], while participants in conventional follow-up were considered compliant when they had sent in at least two of three requested stool samples for calprotectin measurement. Participants were analysed as randomized without imputation of missing data. As previously published web-based programmes have focused on patients with ulcerative colitis,<sup>21–23</sup> we decided a priori to do a subgroup analysis to examine the intervention in two subtypes of IBD, i.e. ulcerative colitis and Crohn's disease. Time-to-flare was plotted in a Kaplan–Meier curve and tested with a two-sided log rank test. We calculated quality-of-life changes scores per group after 52 weeks of follow-up and the proportion of participants per group with a positive change. The cost-effectiveness analysis was performed from a societal perspective [also incorporating costs of travel to the hospital and costs of leave from work of the parents] using unit prices from Dutch Guidelines [see [Supplementary Table 1](#)]. The outcome variables of the cost-effectiveness analysis were the number of relapses within 1 year and the quality-of-life change scores from baseline. Results of 5000 bootstrap replications were calculated using R version 3.2.0 [R Foundation for Statistical Computing] and are presented in a cost-effectiveness plane. Predictors of good adherence to home telemonitoring were assessed by calculating odds ratios with the use of univariate logistic regression analysis. Participants' opinions about the telemonitoring programme are presented as diverging stacked bar charts using Microsoft Excel 2007.<sup>24</sup> All data were analysed electronically using SPSS version 22.0 for Windows [SPSS] and were presented with GraphPad Prism version 5 for Windows [GraphPad Software].

## 2.8. Patient involvement

The Dutch Crohn's and Colitis patient organization [CCUVN] was involved from the inception of the study. The Director was consulted for advice regarding the study design and was on the committee that decided on the ZonMw funding. All participants received a summary of the results.

# 3. Results

## 3.1. Description of participants

Participants were recruited between June 6, 2013 and January 15, 2016. Of 295 teenagers who received information about the study, 170 were eligible and randomly allocated to the home telemonitoring [ $n = 84$ ] or conventional follow-up [ $n = 86$ ] arms [Figure 2]. Baseline characteristics are presented in [Table 1](#). The two trial arms were well balanced except for an overrepresentation of males assigned to home telemonitoring. We did not conduct statistical adjustments for this imbalance. Good compliance to the study protocol [response to  $\geq 80\%$  of automated alerts] was observed in 48 participants [57%] assigned to home telemonitoring and in 72 participants [84%] assigned to conventional follow-up [Figure 2].

## 3.2. Primary outcome

During 52 weeks of follow-up, 28 participants (33%, 95% confidence interval [CI] 24–44%) in the home telemonitoring arm and 29 [34%, 95% CI 24–44%] in the conventional follow-up arm experienced one or more disease flares [Figure 3]. There was no difference in time-to-flare between groups, either in the intention-to-treat analysis or in the per-protocol analysis [respectively  $p = 0.932$  and  $0.908$ ]. Subgroup analysis according to disease type did not show a difference in time-to-flare either [data not shown].

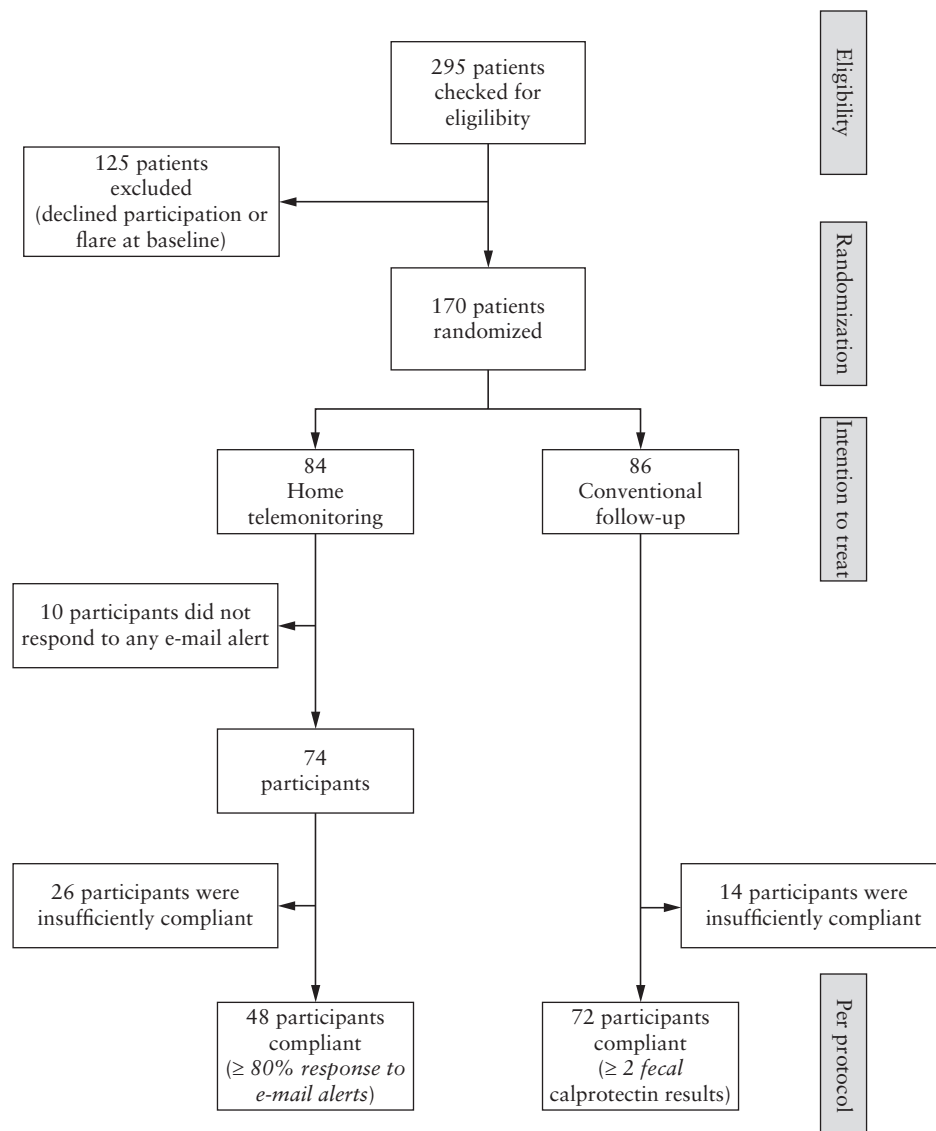
## 3.3. Secondary outcomes

### 3.3.1. Quality of life

In the intention-to-treat analysis, the mean quality-of-life change score from baseline was +1.32 in the home telemonitoring group compared to −0.32 in the conventional follow-up group [ $p = 0.27$ ]. A total of 54% of participants in the home telemonitoring group reported a positive change during 52 weeks of follow-up compared to 44% in the conventional group [ $p = 0.27$ ] [Figure 4].

### 3.3.2. Cost-effectiveness

Participants assigned to home telemonitoring had fewer face-to-face encounters with their care provider compared to those in conventional follow-up [3.6 vs 4.3,  $p < 0.001$ ]. Also, the number of times blood was taken, trips to the hospital and hours of absence from school or social activities were lower in the home telemonitoring group. On the other hand, the total numbers of abdominal sonography studies in participants with Crohn's disease and stool examinations were increased in the telemonitoring group [Supplementary Table 2]. In [Figure 5](#) we present cost-effectiveness planes for the outcomes *total number of relapses* and *quality-of-life change score* after 52 weeks of follow-up, both in an intention-to-treat and per-protocol analysis. Home telemonitoring was cost-effective, as it demonstrated comparable effectiveness with conventional follow-up at lower costs. Home telemonitoring led to a mean annual cost-saving of €89 per participant in the intention-to-treat analysis. The intervention was most cost-saving in participants who were compliant



**Figure 2.** Study flow chart presenting the number of participants who were included in the intention-to-treat and per-protocol analyses. Definition of compliant was  $\geq 80\%$  response to e-mail alerts in the home telemonitoring group and two or more faecal calprotectin measurements in the conventional follow-up group.

to the telemonitoring schedule, corresponding with a mean annual cost-saving of €360 per participant.

### 3.3.3. Predictors of compliance to the home telemonitoring programme

In [Figure 6](#) we show that factors associated with compliance to the home telemonitoring programme were a higher EQ (odds ratio [OR] 1.3, 95% CI 1.1–1.5) and a longer travel distance [OR 1.2, 95% CI 1.0–1.5].

### 3.3.4. Participants' opinion about home telemonitoring

Fifty-nine of 84 participants gave their opinion about participating in the home telemonitoring programme [[Figure 7](#)]. Forty-four respondents [75%] were compliant to 80% or more of the alerts. The majority of respondents agreed that home telemonitoring is time-saving [96%], increased their understanding of the disease [56%] and did not disturb them [79%]. Seventy-one per cent wished to continue with home telemonitoring care.

## 4. Discussion

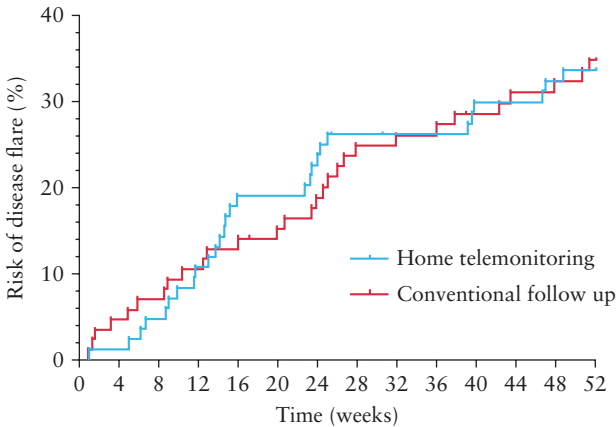
### 4.1. Main findings and relevance

This study shows that calprotectin-based home telemonitoring of teenagers with clinically stable IBD at baseline is a safe and cost-saving alternative to conventional follow-up. The results for the primary outcome [time-to-flare] were not different between the two follow-up strategies, regardless of intention-to-treat or per-protocol analysis. For participants and their parents in the intervention arm, the time-saving aspect of home telemonitoring and the better sense of disease control were highly valued. We postulate that the cost-saving effect of home telemonitoring could have been larger if the Medical Ethical Committee has allowed use of a larger test interval for patients on immunomodulators [complete blood count and liver enzymes] or aminosalicylates [creatinine]. These blood tests were done in the participating IBD centres, and not at the primary care level. Although not evidence-based, many clinicians believe that these tests should be performed with an interval of 3–6 months.<sup>1,25</sup> We are of the opinion that these blood tests can be performed



**Table 1.** Baseline characteristics of participants allocated to home telemonitoring or conventional follow-up; values are percentages [numbers] unless otherwise stated

Characteristic	Home telemonitoring [n = 84]	Conventional follow-up [n = 86]
Median [IQR] age at enrolment, years	15 [12–16]	15 [13–17]
Male gender	64 [54]	45 [39]
Type of disease		
Ulcerative colitis	54 [45]	51 [44]
Crohn's disease	46 [39]	49 [42]
Median [IQR] age at diagnosis, years	12 [9–13]	13 [9–15]
Median [IQR] time since last disease flare, months	13 [7–29]	15 [8–30]
Disease flare in last 12 months before enrolment	46 [39]	42 [36]
Median [IQR] stool calprotectin at enrolment, µg/g	140 [79–408]	160 [100–584]
Taking immunomodulator	69 [58]	65 [56]
Taking aminosalicylate	57 [48]	52 [45]
Emotional quotient		
low [≤89]	5 [4]	5 [4]
average [90–109]	27 [23]	30 [26]
high [≥110]	46 [39]	51 [44]
missing	21 [18]	14 [12]
Median [range] travel distance, km	30 [2–116]	25 [1–142]



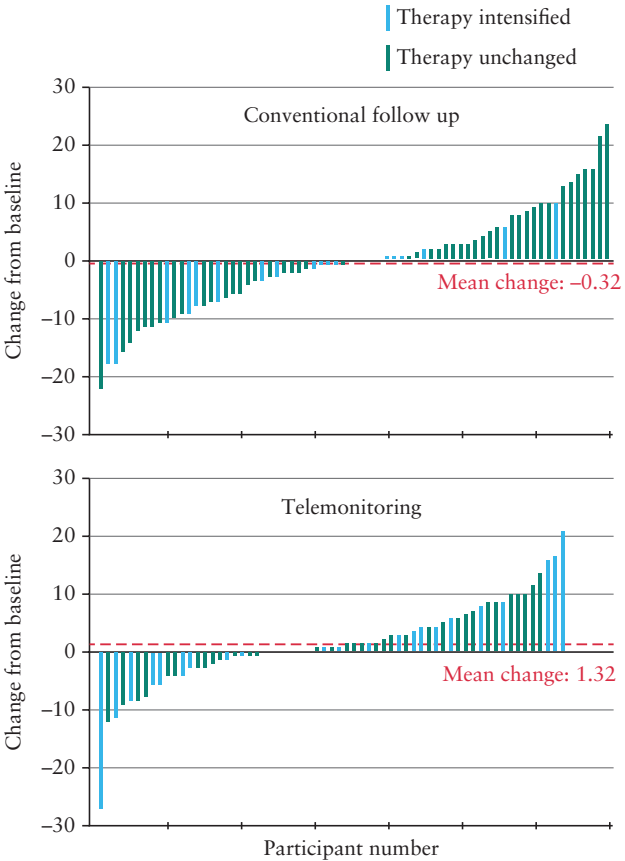
**Figure 3.** Primary outcome: cumulative risk of disease flares in participants assigned to home telemonitoring and conventional follow-up [intention-to-treat analysis].

with wider intervals in teenagers with stable IBD without dose escalations.

In this study we used the flarometer score as a non-invasive estimate of the probability of a disease flare. The flarometer score is a clinical composite score consisting of the participant's answers to a validated disease activity questionnaire and the result of the stool calprotectin test [Figure 1]. The concept of the flarometer was evaluated in a prospective study among teenagers with IBD and had better predictive value than a composite score with C-reactive protein.<sup>26</sup> Home telemonitoring with a non-invasive predictor of disease flare is a fundamental change in the way to follow teenagers with IBD. Schedules for follow-up have traditionally been rigid [e.g. checks in the consultation room of the specialist at fixed intervals], but we have shown that home telemonitoring can move IBD care into a new era in which teenagers take ownership of their chronic disease and participate in the therapeutic decision-making process based on longitudinal tracking of flarometer results.

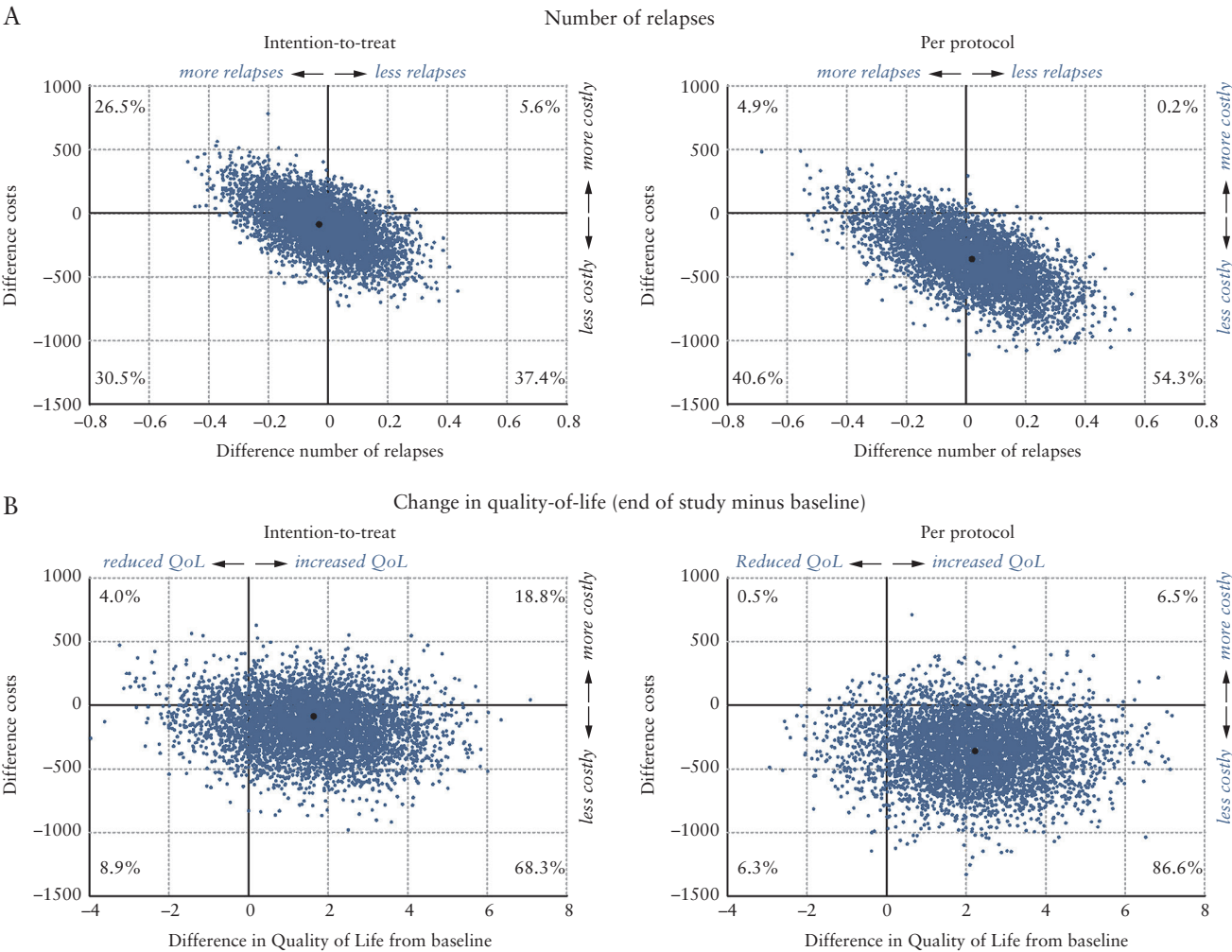
4.2. Comparison with other studies

The results of this multi-centre randomized controlled trial among Dutch teenagers with IBD are consistent with a recently published single-centre study among 53 Danish teenagers with IBD.<sup>27</sup> The

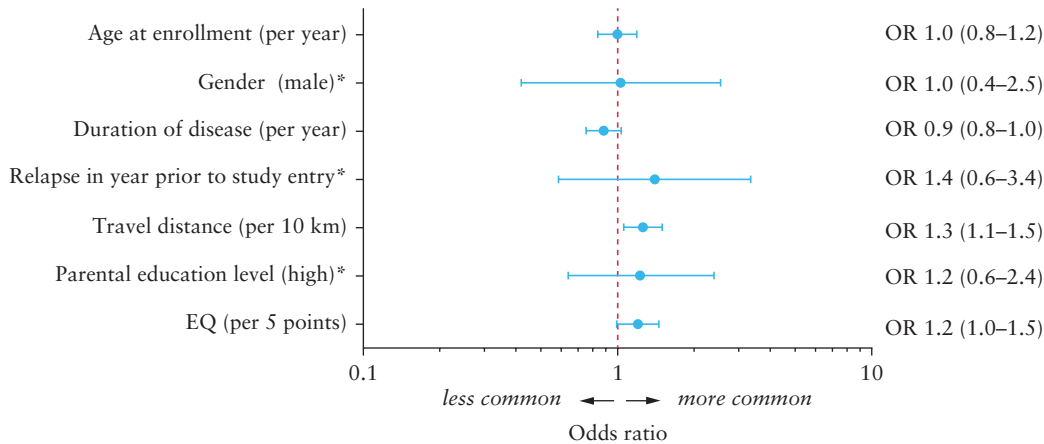


**Figure 4.** Waterfall plot illustrating each participant's change in quality-of-life [IMPACT-III] score during 52 weeks. The horizontal axis across the plot serves as the baseline measure; vertical bars are drawn for each participant. Vertical bars that are below the line represent participants with worsening scores, while bars above the line represent those who experienced improvement of quality-of-life scores. Grey bars represent participants with one or more treatment intensification. Black bars represent those with unchanged treatment.

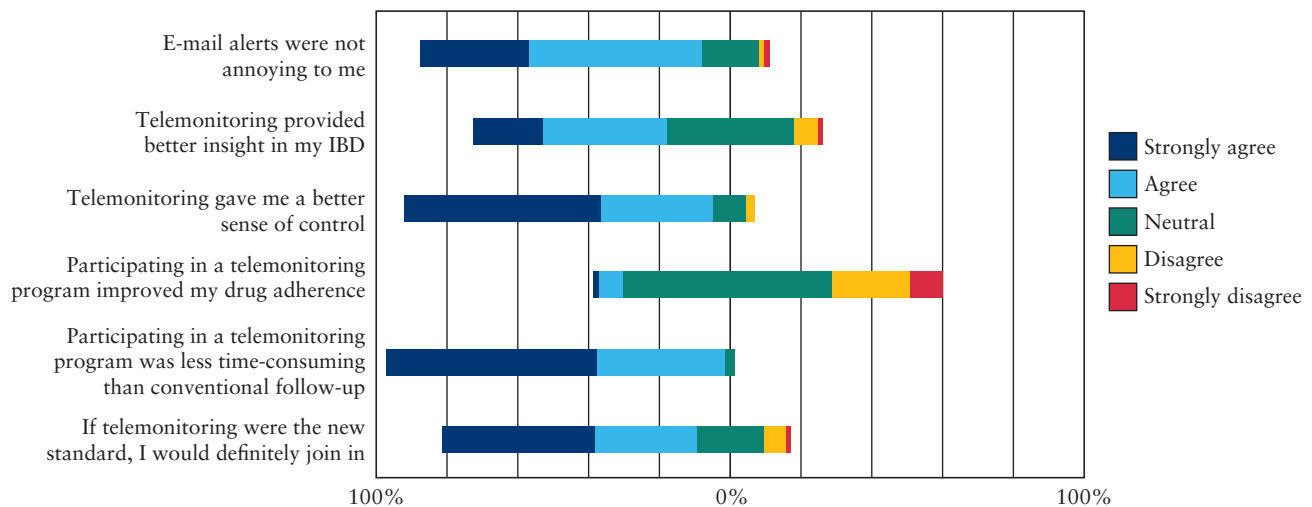
Danish study had a similar design as our study with a longer observation period, but with smaller group size. The authors also concluded that telemonitoring is safe, without causing an increase in



**Figure 5.** Secondary outcome: cost-effectiveness [intention-to-treat and per-protocol analysis]. Planes present total costs and effects for home telemonitoring care compared to conventional follow-up. Positive costs or effects mean home telemonitoring is more expensive or more effective compared to conventional follow-up. Effects in [A] are defined as the total number of relapses and in [B] as the individual change in quality-of-life from baseline to end of the study. The black dots in the middle correlate with the point estimates of our data. Blue diamonds represent the outcome of 5000 bootstrap replications.



**Figure 6.** Odds ratios and 95% confidence intervals for factors associated with better compliance in participants followed by home telemonitoring. Factors with an odds ratio >1 were more common in participants who were compliant to 80% or more of the alerts. \* Binary variables were coded 0 for no, or 1 for yes. High education was defined as pre-university, senior secondary general, university or higher professional level.



**Figure 7.** Participants' opinions about home telemonitoring. The proportion of patients who agreed to the statements [left of the neutral line] vs those who disagreed [right of the neutral line].

disease activity or treatment escalation compared with conventional follow-up.

Both studies showed that not all participants are suitable to be followed in a telemonitoring programme. It is important to realize that differences exist in people's desire for information. Some patients seek as much information as possible about the threat of a disease flare ['monitors'], while others try to avoid potentially threatening information ['blunters'].<sup>28</sup> Home telemonitoring will give the former category of patients and parents a greater sense of control, as opposed to the latter category who may feel more vulnerable due to the constant confrontation with their chronic disease. This aspect may partially explain attrition in the telemonitoring arm. A possible solution to this problem is to position telemonitoring as checks for wellness rather than as temporary reprieves from eventual illness.

### 4.3. Strengths and limitations

In a recent systematic review on eHealth technologies in IBD it was concluded that the majority of published trials had a small sample size, were single-centre and only addressed feasibility.<sup>7</sup> Methodological shortcomings of these studies included heterogeneity of outcome measures, lack of clinician/patient input, lack of validation against conventional symptom scores and limited cost-benefit analyses.<sup>7,29</sup> Our study had a large sample size that enhanced internal validity, whereas the multi-centre recruitment in both academic and general hospitals enhanced external validity. Additionally, we provided data on the effect of telemonitoring on the cumulative incidence of flares and change in quality-of-life and linked these outcomes to costs. We considered direct costs of healthcare delivery, and indirect cost savings [improved parental work productivity and reduced school absenteeism] in the calculation. We are reasonably certain of our effect estimates, as we enrolled a cohort of clinically stable participants that represents approximately 50% of the spectrum of teenage IBD patients. Furthermore, we ran the trial at two levels of hospital care and therefore assume that the annual incidence of disease flares in our study cohort is a true reflection of what happens in the real world.

The results of this randomized controlled trial come from a category of patients and parents who had an interest in home telemonitoring and may not be representative of all teenage IBD patients. In particular, the patients and parents who participated

in the trial may have been more eager to learn about telephone and Internet technologies to monitor disease activity and thus differ in important ways from parents and adolescents who chose not to participate. The most common reason for declining participation was related to a preference for direct contact with the specialist.

Secondly, the participation rate, which is the percentage of eligible participants who eventually participated in the trial, varied considerably per centre. It was highest in the centre that initiated the study [77%] and ranged between 13 and 73% in the other centres. We have no reasons to believe that the interest in telemonitoring among eligible participants varied per centre, but think that the specialist's dedication to the monitoring programme may have varied from centre to centre.

Thirdly, we used a stool calprotectin value below 250 µg/g as a target for disease remission. There is no agreement among IBD experts as to whether these are the optimal thresholds, indicating the need for prospective and randomized studies comparing monitoring strategies that vary in thresholds to strike a balance between under- and over-treatment.

Finally, the use of the flarometer score has limitations as it partly relies on a self-reported symptom score. This was illustrated in three participants who reported high symptom scores together with faecal calprotectin values in the target range. This discrepancy was observed in participants with suspected irritable bowel syndrome and created so much confusion culminating in withdrawing one participant from the experimental arm of the trial on the specialist's advice. This participant continued with conventional follow-up, outside the scope of this study.

### 4.4. Implications for clinicians, patients and policy-makers

The number of telemonitoring initiatives for IBD care is rising.<sup>7,8,21,23,27,30–36</sup> Home telemonitoring is a practical method for follow-up care in teenagers with a relatively stable course of IBD prior to inclusion. A calprotectin drift away from the target range in asymptomatic patients is frequently a prelude to a disease flare within the next 2–3 months, while consecutive normal values are associated with a high probability to remain in remission for the next 2–3 months.<sup>37</sup> Whether pre-emptive treatment of asymptomatic teenagers with increased calprotectin values prevents progression to



an overt flare in the short term and progressive bowel damage in the long term could be the focus of a future trial.

It is a misconception that the use of home telemonitoring to follow disease activity over time will greatly diminish the workload of the specialist, as all generated data must be reviewed critically and, if needed, actions must be taken. To maintain a successful home telemonitoring follow-up programme, a joined collaboration is warranted between motivated patients, parents and specialists.<sup>38,39</sup> Characteristics that were significantly more common among compliant participants were a higher emotional quotient and a long travel distance to the hospital. We hypothesize that the emotionally more mature participants value the better sense of disease control, while those living further away from the hospital value the time-saving aspect of home telemonitoring. We recommend offering the telemonitoring service especially to teenagers who have at least one of these characteristics, and not to those who have a preference for direct contact with the specialist.

Desktop medical activities not linked to a face-to-face contact are currently not reimbursable under typical fee-for-service contractual and regulatory arrangements. Home telemonitoring activities such as described in this project – reviewing generated data and responding to patients' emails – are of high value to the delivery system and to patients, so the design of gastroenterology practices and reimbursement policies should reflect this value.

Home telemonitoring is attractive for teenagers and their families, and health professionals may be interested in using it to keep teenagers who are well out of hospital and to ease the pressure on overstretched outpatient services.

## 5. Conclusions

Follow-up of teenagers with IBD by home telemonitoring is as safe as conventional follow-up, and reduces outpatient visits and societal costs. The positive impact on quality-of-life was similar in the two groups.

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## Conflict of Interest

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## Author Contributions

Guarantor of the article: PFvR. PvR conceived the study. AH, HG, AMK, JR, HJV and PFvR initiated the study design, and AD helped with implementation. PFvR is the grant holder. HG provided statistical expertise in clinical trial design and cost-effectiveness analysis. AH conducted the primary statistical analysis. AK, FK, TdM, ON, RKW, MW, TH, JE, HvW, DL and LM gave input to the design [KiCC meetings] and recruited patients from their clinic. AH, AD and PFvR drafted the first version of the article. All other authors revised the article critically for important intellectual content. All authors have approved the final version of the article, including the authorship list.

## Supplementary Data

Supplementary data are available at ECCO-JCC online.

## References

1. Ruemmele FM, Veres G, Kolho KL, *et al.*; European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis* 2014;8:1179–207.
2. Henriksen M, Jahnsen J, Lygren I, *et al.*; IBSEN Study Group. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study). *Inflamm Bowel Dis* 2006;12:543–50.
3. Henriksen M, Jahnsen J, Lygren I, *et al.*; Ibsen Study Group. Clinical course in Crohn's disease: results of a five-year population-based follow-up study (the IBSEN study). *Scand J Gastroenterol* 2007;42:602–10.
4. Kappelman MD, Moore KR, Allen JK, Cook SF. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. *Dig Dis Sci* 2013;58:519–25.
5. Romberg-Camps MJL, Hesselink-van de Kruijs MAM, Schouten LJ, *et al.* Inflammatory bowel disease in South Limburg (the Netherlands) 1991–2002: Incidence, diagnostic delay, and seasonal variations in onset of symptoms. *J Crohns Colitis* 2009;3:115–24.
6. Malmberg P, Hildebrand H. The emerging global epidemic of paediatric inflammatory bowel disease—causes and consequences. *J Intern Med* 2016;279:241–58.
7. Jackson BD, Gray K, Knowles SR, De Cruz P. EHealth technologies in inflammatory bowel disease: a systematic review. *J Crohns Colitis* 2016;10:1103–21.
8. de Jong MJ, van der Meulen-de Jong AE, Romberg-Camps MJ, *et al.* Telemedicine for management of inflammatory bowel disease (myIBD-coach): a pragmatic, multicentre, randomised controlled trial. *Lancet* 2017;390:959–68.
9. Cole R, Ashok D, Razack A, Azaz A, Sebastian S. Evaluation of outcomes in adolescent inflammatory bowel disease patients following transfer from pediatric to adult health care services: case for transition. *J Adolesc Health* 2015;57:212–7.
10. Heida A, Dijkstra A, Groen H, Muller Kobold A, Verkade H, van Rheeën P. Comparing the efficacy of a web-assisted calprotectin-based treatment algorithm (IBD-live) with usual practices in teenagers with inflammatory bowel disease: study protocol for a randomized controlled trial. *Trials* 2015;16:271.
11. Levine A, Koletzko S, Turner D, *et al.*; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2014;58:795–806.
12. Escher JC, Hagemeyer JW, de Ridder L, Rings EHHM. Guideline on diagnosis and treatment of pediatric IBD. <http://www.nvk.nl/Portals/0/>

- [richtlijnen/inflammatoire darmziekten/ inflammatoiredarmziekten.pdf](#). Accessed September 1, 2017.
13. Turner D, Otley AR, Mack D, *et al*. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology* 2007;133:423–32.
  14. Hyams JS, Ferry GD, Mandel FS, *et al*. Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr* 1991;12:439–47.
  15. Kappelman MD, Crandall WV, Colletti RB, *et al*. Short pediatric Crohn's disease activity index for quality improvement and observational research. *Inflamm Bowel Dis* 2011;17:112–7.
  16. Coorevits L, Baert FJ, Vanpoucke HJ. Faecal calprotectin: comparative study of the Quantum Blue rapid test and an established ELISA method. *Clin Chem Lab Med* 2013;51:825–31.
  17. Otley A, Smith C, Nicholas D, *et al*. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2002;35:557–63.
  18. Otley A. *IMPACT-III: User's Guide 2005*.
  19. Loonen HJ, Grootenhuys MA, Last BF, de Haan RJ, Bouquet J, Derkx BH. Measuring quality of life in children with inflammatory bowel disease: the impact-II (NL). *Qual Life Res* 2002;11:47–56.
  20. Bar-On R, Parker J. Bar-on emotional quotient inventory: youth version (EQ-i:YV): technical manual. *Toronto Multi-Health Syst* 2008.
  21. Cross RK, Cheevers N, Rustgi A, Langenberg P, Finkelstein J. Randomized, controlled trial of home telemanagement in patients with ulcerative colitis (UC HAT). *Inflamm Bowel Dis* 2012;18:1018–25.
  22. Cross RK, Finkelstein J. Challenges in the design of a Home Telemanagement trial for patients with ulcerative colitis. *Clin Trials* 2009;6:649–57.
  23. Elkjaer M, Shuhaibar M, Burisch J, *et al*. E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach. *Gut* 2010;59:1652–61.
  24. Heiberger RM, Robbins NB. Design of diverging stacked bar charts for likert scales and other applications. *J Stat Softw* 2014;57:1–32.
  25. Turner D, Levine A, Escher JC, *et al*.; European Crohn's and Colitis Organization; European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:340–61.
  26. van Rheeën PF. Role of fecal calprotectin testing to predict relapse in teenagers with inflammatory bowel disease who report full disease control. *Inflamm Bowel Dis* 2012;18:2018–25.
  27. Carlsen K, Jakobsen C, Houen G, *et al*. Self-managed eHealth disease monitoring in children and adolescents with inflammatory bowel disease: a randomized controlled trial. *Inflamm Bowel Dis* 2017;23:357–65.
  28. Michie S, McCaffry K, Heneghan C. Monitoring as a learning and motivational tool. In: Glasziou PP, Irwig L, Aronson JK, editors. *Evidence Based Medical Monitoring from Principles to Practice*. Oxford: Blackwell Publishing; 2008: 123–39.
  29. Bossuyt P, Pouillon L, Peyrin-Biroulet L. Primetime for e-health in IBD? *Nat Rev Gastroenterol Hepatol* 2017;14:133–4.
  30. Hommel KA, Gray WN, Hente E, *et al*. The Telehealth Enhancement of Adherence to Medication (TEAM) in pediatric IBD trial: Design and methodology. *Contemp Clin Trials* 2015;43:105–13.
  31. Cross RK, Jambaulikar G, Langenberg P, *et al*. TELEmedicine for Patients with Inflammatory Bowel Disease (TELE-IBD): Design and implementation of randomized clinical trial. *Contemp Clin Trials* 2015;42:132–44.
  32. Pedersen N, Thielsen P, Martinsen L, *et al*. eHealth: individualization of mesalazine treatment through a self-managed web-based solution in mild-to-moderate ulcerative colitis. *Inflamm Bowel Dis* 2014;20:2276–85.
  33. Pedersen N, Elkjaer M, Duricova D, *et al*. eHealth: individualisation of infliximab treatment and disease course via a self-managed web-based solution in Crohn's disease. *Aliment Pharmacol Ther* 2012;36:840–9.
  34. Krier M, Kaltenbach T, McQuaid K, Soetikno R. Potential use of telemedicine to provide outpatient care for inflammatory bowel disease. *Am J Gastroenterol* 2011;106:2063–7.
  35. Vinding KK, Elsberg H, Thorkilgaard T, *et al*. Fecal calprotectin measured by patients at home using smartphones—a new clinical tool in monitoring patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2016;22:336–44.
  36. Heida A, Knol M, Kobold AM, Bootsman J, Dijkstra G, van Rheeën PF. Agreement between home-based measurement of stool calprotectin and ELISA results for monitoring inflammatory bowel disease activity. *Clin Gastroenterol Hepatol* 2017;15:1742–1749.e2.
  37. Heida A, Park KT, van Rheeën PF. Clinical utility of fecal calprotectin monitoring in asymptomatic patients with inflammatory bowel disease: a systematic review and practical guide. *Inflamm Bowel Dis* 2017;23:894–902.
  38. Mäse LC, Watts AW, Barr SI, *et al*. Individual and household predictors of adolescents' adherence to a web-based intervention. *Ann Behav Med* 2015;49:371–83.
  39. Fedele DA, Cushing CC, Fritz A, Amaro CM, Ortega A. Mobile health interventions for improving health outcomes in youth: a meta-analysis. *JAMA Pediatr* 2017;171:461–9.