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Cost-effectiveness of physiotherapy in childhood functional constipation: a randomized controlled trial in primary care

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Abstract

Objective: Health care expenditures for children with functional constipation (FC) are high, while conservative management is successful in only 50% of the children. The aim is to evaluate whether adding physiotherapy to conventional treatment (CT) is a cost-effective strategy in the management of children with FC aged 4–18 years in primary care.

Methods: A cost-effectiveness analysis was performed alongside a randomized controlled trial (RCT) with 8-month follow-up. Costs were assessed from a societal perspective, effectiveness included both the primary outcome (treatment success defined as the absence of FC and no laxative use) and the secondary outcome (absence of FC irrespective of laxative use). Uncertainty was assessed by bootstrapping and cost-effectiveness acceptability curves (CEACs) were displayed.

Results: One hundred and thirty-four children were randomized. The incremental cost-effectiveness ratio (ICER) for one additional successfully treated child in the physiotherapy group compared with the CT group was €24,060 (95% confidence interval [CI] €–16,275 to €31,390) and for the secondary outcome €1,221 (95% CI €–12,905 to €10,956). Subgroup analyses showed that for children with chronic laxative use the ICER was €2,134 (95% CI –24,975 to 17,192) and €571 (95% CI 11 to 3,566), respectively. At a value of €1,000, the CEAC showed a probability of 0.53 of cost-effectiveness for the primary outcome, and 0.90 for the secondary outcome.

Conclusions: Physiotherapy added to CT as first-line treatment for all children with FC is not cost-effective compared with CT alone. Future studies should consider the cost-effectiveness of physiotherapy added to CT in children with chronic laxative use.

Trial registration: The RCT is registered in the Netherlands Trial Register (NTR4797), on the 8th of September 2014. The first child was enrolled on the 2nd of December 2014. https://www.trialregister.nl/trial/4654.

Key words: child, constipation, cost-effectiveness, physical therapy, primary care, randomized controlled trial

Key Messages

- Health care costs for children with functional constipation (FC) are high.
- Physiotherapy is not cost-effective for all children with FC.
- In children with chronic FC adding physiotherapy is worth considering.
- The cost-effectiveness in children with chronic FC needs further evaluation.
- The definition of treatment success influences the study outcomes.

Introduction

Functional constipation (FC) is a common condition among children, the prevalence ranged from 0.5% to 32.2% with a pooled prevalence of 9.5% (95% confidence interval [CI] 7.5–12.1).[1] Children with FC suffer from bothersome and frustrating symptoms which negatively affect their quality of life and that of their families.[2–6] Conventional treatment (CT) includes education, dietary advice, toilet training, and prescription of laxatives.[7,8] The quality of the evidence of the efficacy of laxatives and adherence to CT is low.[9–12] Half of the children diagnosed with constipation are still struggling with this problem after 6–12-month treatment, and a quarter of the children continue to experience symptoms even into adulthood.[13,14]

The high prevalence and chronic character of constipation in children result in high health care costs.[1,15–17] In the United States, the direct yearly health care costs for children with FC were 3 times higher compared with children without FC ($3,362 vs $1,095).[15] Most costs are related to consultations (general practitioners [GPs] and paediatricians), emergency room visits, and laxatives.[15,16] These high direct health care costs remain consistent during the entire childhood.[16] In addition, FC causes higher indirect costs as children with constipation miss more school days, and parents lose workdays.[15]

Two small randomized controlled trials (RCTs) have shown positive effects of adding physiotherapy to CT in childrenn referred to a hospital setting.[18,19] Treatment early in the disease process may increase treatment success and therewith reduce health care utilization and costs. To test this hypothesis, we conducted a pragmatic RCT in primary care evaluating the effectiveness of physiotherapy added to CT compared with CT alone.[20]

Information regarding the cost-effectiveness of physiotherapy added to CT in children with FC is lacking. Therefore, we have performed a cost-effectiveness analysis (CEA) alongside the RCT. Although the RCT showed no differences between groups in treatment success for all children with FC, a CEA is valuable because differences in costs might exist between treatment groups. The aim of this study is to evaluate the cost-effectiveness of physiotherapy plus CT compared with CT alone for children with FC aged 4–18 years presenting in primary care. In addition, we evaluated the cost-effectiveness of physiotherapy for the subgroup of children with chronic laxative use.

Methods

Cost-effectiveness overview

The balance between costs and effects in the physiotherapy plus CT group was evaluated in comparison to the CT only group in a CEAs, and presented in cost-effectiveness planes (CE planes) and cost-effectiveness acceptability curves (CEACs). The CEA was conducted from a societal perspective, indicating that all costs and consequences of the competing interventions are taken into account regardless of who pays for or benefits from them.[21] We performed the CEAs evaluating two definitions of treatment success. Since the time horizon of this study was shorter than 1 year, costs and effects were not discounted.

The design of the RCT and the results of the clinical effectiveness analysis have been published elsewhere.[20,22] The trial was approved by the Medical Ethical Board of the University Medical Center of Groningen (METC2013/331) and was registered in the Netherlands Trial Register (NTR4797). We obtained written informed consent from both parent(s). In addition, children aged ≥12 years also gave informed consent themselves.

Design of the pragmatic RCT

Setting, participants, and randomization

Children were recruited in primary care and paediatric outpatient departments in the Netherlands between 10 September 2014 and 1 March 2017 and last follow-up data were received on 30 November 2017. Inclusion criteria were: age 4–18 years, and a diagnosis of FC by the GP.

Children were randomly allocated in a 1:1 ratio to the two treatment groups. Randomization was stratified according to age (4–8 and 9–18 years). Given the design of the study, we could not blind children, parents, physicians, and physiotherapists to group allocation, but physicians and physiotherapists were blinded to the questionnaire answers.[23]

Interventions

CT only

Children in the control group received CT, which was not restricted with respect to content and number of consultations and dosage of laxatives. GPs and paediatricians were instructed to adhere to the Dutch clinical guidelines for FC in children.[7,8]

Physiotherapy plus CT

Children in the intervention group received CT plus physiotherapy. The physiotherapy consisted of a maximum of nine half-hour sessions carried out by specialist physiotherapists.[20,22]

Health outcomes

The primary outcome was treatment success defined as "the absence of FC according to the Rome III criteria *and* no laxative use in the four weeks prior to measurement." The secondary outcome was "absence of FC irrespective of laxative use." "Absence of FC" was measured with the Questionnaire on Pediatric Gastrointestinal Symptoms Rome-III (QPGS-Rome III).[24] We modified the questionnaire to evaluate symptoms over a 4-week period instead of a 2-month period.

Costs analysis

A societal perspective incorporates direct health care costs, direct nonhealth care costs, and indirect costs due to FC. Data on costs were collected with two questionnaires, and completed by parents

at baseline and after 4- and 8-month follow-up. Direct health care and direct nonhealth care costs related to FC were collected with an adapted version of the Institute of Medical Technology Assessment Medical Consumption Questionnaire (iMTA-MCQ) and indirect costs related to FC with an adapted version of the Productivity Costs Questionnaire (iMTA-PCQ).[25,26] Only questions related to potential differences in costs between the two interventions were included. In the physiotherapy group, the number of consultations to the physiotherapist was recorded by the physiotherapist.

Relevant direct health care costs that were taken into account were costs for consultations and hospitalizations related to FC and medication prescriptions (such as laxatives). Patient and family costs (direct nonhealth care costs) were costs for faecal incontinence materials (such as diapers or mattress protectors), diet supplements, and alternative drugs and treatments. Indirect costs were costs related to work absenteeism of parents. All costs are presented in euros (€) at the price level of 2017, and calculated according to the Dutch cost manual.[27] Table 2 presents a detailed overview of the cost components included and the cost prices used. In principle, we adhered to the national guidelines for cost-effectiveness studies of the Care Institute Netherlands for the pricing of all items including productivity costs.[21] To test the robustness of the cost outcomes, we performed univariate and multivariate sensitivity analyses in which we increased or decreased the cost prices of the three main cost items with 20%.

Cost-effectiveness analysis

An incremental CEA was undertaken to compare CT only vs physiotherapy plus CT over an 8-month time horizon. Only patients with a complete follow-up, i.e. a measurement at 4 and 8 months, were included in the CEA. If a child or parent had completed both cost questionnaire, but a specific cost item was missing, this cost was imputed at item level by imputing the mean of that item in the allocated group. In seven patients, costs at 4-month follow-up were measured over a 3-month period instead of a 4-month period. In these patients, costs were extrapolated to be representative for a 4-month period.

An incremental cost-effectiveness ratio (ICER) represents the additional costs that one intervention imposes over another, compared with the additional effects it delivers.[21] We calculated ICERs by dividing the difference in costs between the intervention and control group by the difference in effectiveness between both treatment groups. The ICER can be interpreted as the *additional* costs needed to treat one *extra* patient successfully. To calculate this, for each of the bootstrapped trial sets, means of costs and outcomes were multiplied by 100. To explore the uncertainty in the CEA, we employed a nonparametric bootstrapping technique with 5,000 replications to estimate CIs. Results of the bootstraps are presented in CE planes and CEACs. A CEAC is based on the uncertainty in cost and effect differences and shows the probability that the alternative (new) intervention is cost-effective over a range of possible values (thresholds), that a decision maker might be willing to pay for one additional unit of effect.

A predefined subgroup analysis was performed to evaluate the cost-effectiveness of the intervention for children with chronic laxative use. We defined chronic laxative use as continuous or regular laxative use (≥3 periods) in the 12 months before enrolment.

Data were analysed using SPSS Version 25.0 (IBM Corp., Armonk, NY). For bootstrapping we used Microsoft Excel 2010.

Results

In total, 134 children were included in the RCT, of which 100 children (75%) were included in the complete case analyses (Supplementary Fig. 1). Baseline characteristics of children in the intervention and control group were comparable (Table 1). In addition, children lost to follow-up (n = 32) and completers (n = 100) were comparable with respect to baseline characteristics and baseline health care costs.

Table 2 presents the mean costs per child during the 8-month follow-up period. Mean costs per child were €380 (95% CI €289–480) in the physiotherapy plus CT group and €226 (95% CI €111–368) in the CT only group. The mean costs for the physiotherapy intervention were €206 (95% CI 180–227) per child. Without taking these physiotherapy intervention costs into account, total costs were slightly lower in the intervention group (€174) compared with the CT group (€226), differences in costs per sector were: health care costs (€122 vs €131), patient and family costs (€30 vs €41), and indirect costs (€22 vs €53) per child.

In the main analysis, the total costs were €155 higher in the intervention group compared with the control group. The results of the univariate and multivariate sensitivity analyses did not have a large

Table 1. Baseline characteristics of children (n = 134) with FC in primary care (2014–2017).

	CT (n = 67)	Physiotherapy plus CT (n = 67)
Age (in years), mean (SD)	7.8 (3.5)	7.3 (3.4)
Girls (n, %)	44/67 (66%)	38/67 (57%)
Chronic laxative use[a] (n, %)	31/58 (53%)	41/57 (72%)
Previous episodes of FC (n, %)		
≥2	42/64 (66%)	43/61 (71%)
1	3/64 (5%)	4/61 (7%)
0	19/64 (30%)	14/61 (21%)
Use of laxatives in previous 4 weeks (n, %)	44/59 (75%)	46/56 (82%)
Abdominal pain/discomfort ≥ once a week (n, %)	41/67 (61%)	35/66 (53%)
Constipation related symptoms and signs (Rome III criteria)		
≤2 defecations in the toilet per week (n, %)	10/67 (15%)	16/67 (24%)
Faecal incontinence ≥1 per week(n, %)	34/67 (50%)	26/67 (39%)
Stool withholding (n, %)	18/67 (27%)	22/67 (33%)
Painful or hard bowel movements (n, %)	46/67 (69%)	51/67 (76%)
Large faecal mass in the abdomen or rectum (n, %)	38/67 (57%)	36/67 (54%)
Large stools that obstruct the toilet (n, %)	12/67 (18%)	11/67 (16%)

[a]Chronic laxative use was defined as continuous or regular laxative use (≥3 periods) in the 12 months before inclusion.

Table 2. Mean costs (95% CI) and mean differences in costs between physiotherapy plus CT group and CT group alone during the 8-month follow-up period (complete cases *n* = 100).

Types of costs	Unit price 2017 (€)	Source	Mean costs CT (95% CI) *N* = 48	Mean costs physio plus CT (95% CI) *N* = 52	Mean difference (95% CI)
Health care costs					
GP	33.76 per consultation	CQ	27 (12 to 47)	9 (4 to 14)	−16 (−39 to −2)
Paediatrician	103.34 per consultation	CQ	19 (6 to 38)	38 (17 to 62)	19 (−10 to 46)
Physiotherapist	33.76 per consultation	RP/CQ[c]	4 (1 to 9)	206 (180 to 227)	201 (175 to 223)
Other health care professional	Variable[a]	CQ	43 (8 to 95)	33 (11 to 61)	−9 (−67 to 35)
Laxatives	Variable[b]	CQ	37 (21 to 57)	42 (16 to 68)	5 (−31 to 54)
Other health care costs (e.g. pain medication, hospitalization)	Variable	CQ	1 (0 to 2)	0 (—)	−1 (−2 to 0)
Subtotal health care costs			131 (75 to 204)	328 (256 to 412)	196 (92 to 301)
Patient and family costs					
Non-health care costs (diapers, underpants, mattress protector)	Patient reported costs	CQ	23 (5 to 49)	22 (3 to 49)	−1 (−33 to 32)
Additional diet supplements	Patient reported costs	CQ	12 (1 to 32)	7 (0 to 17)	5 (−28 to 32)
Alternative medicine costs	Patient reported costs	CQ	5 (0 to 12)	1 (0 to 1)	4 (−12 to 0)
Alternative treatment costs	Patient reported costs	CQ	1 (0 to 3)	0 (—)	−1 (−3 to 0)
Subtotal patient and family costs			41 (12 to 80)	30 (7 to 59)	−11 (−57 to 30)
Indirect costs					
Work absenteeism parents	35.55 per h	CQ	53 (0 to 139)	22 (0 to 59)	−31 (−122 to 38)
Subtotal indirect costs			53 (0 to 139)	22 (0 to 59)	−31 (−122 to 38)
Total costs all sectors			226 (111 to 368)	380 (289 to 480)	155 (−12 to 310)

CQ, cost questionnaire; h, hour; RP, registration physiotherapist. The unit price is based on the Dutch cost manual.

[a]Other health care professionals costs: out of hours service GP (€110.50 per consultation), other medical specialist (€93.11 per consultation), emergency department (€264.99 per consultation), and psychologist (€65.48 per consultation).

[b]Prices are shown per gram: Forlax (€0.05), ForlaxJR (€0.06), Movicolon (€0.01), Macrogol (€0.05), Psyllium fibres (€0.08), magnesium oxide (€0.0022 per µg), lactulose (€0.004 per mL), and sodium picosulfate (€0.25 per defined daily dose).

[c]In the intervention group, we used the number of consultations reported by the physiotherapist on the registration form, in the control group we used the number of consultations reported by parents in the cost questionnaire because those children were not referred to physiotherapy by a member of the research team, and therefore physiotherapists were not instructed to use the RP form.

Table 3. Results of cost-effectiveness analyses based on complete case analyses (*n* = 100).

	Effects			ICER	Alternative 95% CI	Distribution (%) cost-effectiveness plane quadrants			
	CT (*n* = 48)	Physio plus CT (*n* = 52)	Mean differences (alternative 95% CI)		2.5–97.5	North east ☹☺	North west ☹☹	South west ☺☹	South east ☺☺
Absence of FC *and* no laxatives (*n*, %)	20 (42)	22 (42)	0.64 (−0.17 to 0.22)	24,060[a]	−16,275 to 31,390	50	46	1	3
Absence of FC (*n*, %)	30 (63)	38 (75)	12.01 (11.76 to 12.26)	1,221[a]	−12,905 to 10,956	85	11	0	4

[a]ICERs are displayed in additional costs to treat one extra person successful. The blue smiley is related to the costs and the green one to the effects of physiotherapy plus CT compared with CT alone. Thus, the north-east quadrant means physiotherapy plus CT is more effective, but more costly than CT alone, the north-west quadrant physiotherapy plus CT is less effective and more costly than CT alone, the south west quadrant physiotherapy plus CT is less effective, but less costly than CT alone, the south east quadrant physiotherapy plus CT is more effective and less costly than CT alone.

impact on this difference in total costs between groups. The differences in costs ranged between €113 and €195 in the multivariate analyses.

After 8 months, the percentages of successfully treated children according to the primary outcome (no FC and no laxatives), and according to the secondary outcome (no FC irrespective of laxative use) were 42% and 75% in the physiotherapy plus CT group and 42% and 63% in the CT group, respectively (Table 3).

The CEA showed an ICER of €24,060 (95% CI −16,275 to 31,390). This means, the incremental cost of treating one additional child successfully with physiotherapy plus CT compared with CT alone is €24,060 (95% CI €−16,275 to €31,390) (Table 3). Fifty percent of the bootstrap simulations were in the north-east quadrant, indicating that they represented a better outcome and higher costs, and 46% were in the north-west quadrant, representing a worse outcome and higher costs (Fig. 1a). The CEA curve (Supplementary Fig. 2a) shows for a number of potential willingness to pay values the probability that physiotherapy plus CT is cost-effective; the maximum probability was 0.53. Results of the sensitivity analyses were unlikely to change the conclusions.

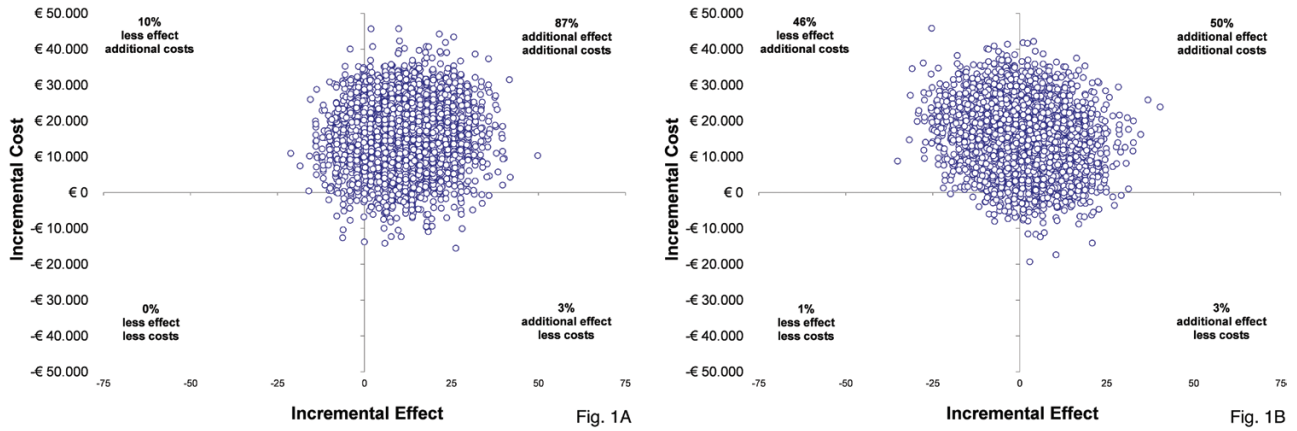

Fig. 1. Incremental cost-effectiveness (CE) planes for the total sample ($n = 100$): 5,000 bootstrap replications for the mean difference between costs and effects. In the cost-effectiveness planes, the differences in costs were shown on the horizontal axis and differences in treatment effects on the vertical axes. In (a) treatment success is defined as no FC and no laxative use; and in (b) as no FC irrespective of continued laxative use. In order to show the costs per additional successfully treated child costs and treatment success rates were multiplied by 100. As an example, bootstrapped cost-effectiveness pairs located in the north-east quadrant showed physiotherapy plus CT to be more effective, but more costly than CT alone, and bootstrapped cost-effectiveness pairs located in the north-west quadrant showed physiotherapy plus CT is less effective and more costly than CT alone.

Table 3 and Fig. 1b show that the ICER to gain one additional patient without FC irrespective of the use of laxatives was €1,221 (95% CI −12,905 to 10,956). The CEA curve (Supplementary Fig. 2b) shows a maximum probability of physiotherapy plus CT being cost-effective of 0.90. If society is willing to pay an extra €500 or €1,000 the probability that physiotherapy plus CT is cost-effective compared with CT is, respectively, 0.47 and 0.90.

In Supplementary Table 1, the costs and effects and the results of the CEAs in the subgroup of children with chronic laxative use are shown. The difference in treatment success percentages was for the primary and secondary outcome, respectively, 10% (95% CI −17% to 37%) and 36% (95% CI 11% – 61%) in favour of the physiotherapy plus CT group. Societal costs related to FC were for the CT group €139 (51–274) and for the physiotherapy plus CT group €364 (95% CI 249–505) in 8 months.

Most of the bootstrap replications for the primary outcome (76%), and almost all replications for the secondary outcome (98%) were in the north-east quadrant, indicating more effects but at higher costs, resulting in an ICER of €2,134 and €571, respectively. The maximum probability physiotherapy added to CT is cost-effective compared with CT alone in children with chronic laxative use was 0.77 according to the primary outcome, and 0.98 according to the secondary outcome. If society is willing to pay an extra €500 or €1,000 euro the probability that physiotherapy plus CT is cost-effective compared with CT alone according to the primary outcome is, respectively, 0.12 and 0.24 and according to the secondary outcome 0.45 and 0.81.

Discussion

Adding physiotherapy to CT in the treatment of all children with FC in primary care is not considered cost-effective compared with CT alone according to the primary outcome. Currently, in the Netherlands there is no explicit cost-effectiveness threshold for our primary as well as our secondary outcome. Therefore, a firm conclusion regarding cost-effectiveness of physiotherapy plus CT cannot be drawn. However, regardless of the maximum amount of money society would be willing to pay, the probability that physiotherapy added to CT will be cost-effective compared with CT alone according to the primary outcome will not exceed 0.5. In case treatment success is defined according to the secondary outcome, the maximum probability that physiotherapy added to CT will be successful is 0.90. If society is willing to pay an incremental cost of €500 or €1,000 the probability that physiotherapy added to CT is cost-effective compared with CT alone is, respectively, 0.47 and 0.90. The ICER showed that the cost-effectiveness of physiotherapy added to CT seems to be larger for children with chronic laxative use. However, this was less obvious in the CEAC analyses, which are based on the uncertainty in cost and effect differences. Further evaluation in children with chronic laxative use is needed.

In the literature treatment, success is recommended as primary outcome in studies investigating childhood FC, however, there is no agreement on the definition of treatment success.[28,29] A strength of this study is that we have used two frequently used definitions of treatment success: “the absence of FC and no laxatives,” and “the absence FC irrespective of laxative use.” The definition of treatment success affected the results and conclusions of our CEAs. In future meta-analyses, this impact of the definition of treatment success on the results of (cost)-effectiveness analyses needs to be taken into consideration.

To our knowledge this is the first study that evaluated the cost-effectiveness of an intervention in children with FC. Therefore, there is no way to set the cost-effectiveness of the physiotherapy intervention against cost-effectiveness of other interventions for the management of childhood FC. In agreement with the literature this study showed that—setting aside costs for physiotherapy—consultations to the GP, paediatrician, and costs for laxatives were the most prominent direct health care costs.[15,16] In our study, we only took into account those costs that were potentially different between interventions, and therefore, fixed health care costs, such as registration costs in general practice, were not taken into account. Furthermore, although we measured indirect costs due to school absenteeism of the child, such as hiring a babysitter, these costs were not included in our analyses as there is no clear policy for the inclusion of these kind of costs. In this study, these costs were negligible.

This study was powered on clinical outcomes and not on cost-effectiveness. However, this is almost never the case in cost-effectiveness studies performed alongside clinical trials because

many more participants are needed for a sufficient power of 80% due to the skewed nature of costs. From an ethical point of view this would not be acceptable. To include more information regarding uncertainty, we applied bootstrapping and present uncertainty in the cost-effectiveness planes using alternative 95% CIs. Uncertainty is also represented in the CEACs and the outcomes of the sensitivity analyses.

The current time horizon was limited to the duration of the follow-up of the trial. One of the advantages of this approach is that it enables collection of both costs and clinical outcomes in detail and on a patient level. Short-term outcomes are therefore rather precise. As participation in studies is time consuming for participants, long-term estimations usually have to rely on assumptions and modelling approaches.

Data regarding health care consumption and productivity were collected using a self-assessed questionnaire. This might induce a self-report bias, however, we think the precision in the cost estimation outweighs this bias, as compared with only using officially registered data. Moreover, since we depend on incremental costs, this bias would be comparable between groups.

We have not presented the results of the cost–utility analysis because the analysis showed that the adult tariffs were not reliable as a proxy for the child tariffs. In fact, the cost–utility analysis showed that a substantial part of the utility scores based on the adult tariffs were below zero, indicating a very low QoL, while parents reported on another QoL question with a scale of 0–100 a mean health status of 85 for their child.

In this study we defined children with chronic laxative use as children with continuous or regular laxative use (≥3 periods) for over 12 months. We did not measure the exact period a child had symptoms and used laxatives. More research is needed to investigate whether duration of symptoms is related to the effects of physiotherapy, and whether there might be an optimal timing for starting physiotherapy. This is of relevance for the CEA in the subgroup population.

Previous studies showed that health care costs for children with FC are higher than for children without FC during their entire childhood and that children (and their parents) do often search for alternative therapies when a child does not respond to laxatives.[16,30] The time horizon of this study was limited to 8 months, which is too short to evaluate whether physiotherapy has an effect on the number of relapses or recurrences, which might influence long-term costs. Future research has to evaluate whether physiotherapy might reduce long-term health care costs.

In conclusion, physiotherapy treatment for all children with FC in primary care is not considered cost-effective. For children with chronic laxative use, the cost-effectiveness of physiotherapy needs further evaluation.

Supplementary material

Supplementary material is available at *Family Practice* online.

Supplementary Table 1. Overview of mean costs and effects and results of cost-effectiveness analyses in subgroup of children with chronic laxative use.

Supplementary Fig. 1. Flowchart of participant flow. FC, functional constipation; GP, general practitioner. [a]Reasons for not receiving physiotherapy were: time constraints of parents/children (n = 2), free of symptoms at time of physiotherapy appointment (n = 1), not showing up at the appointment without a reason (n = 3).

Supplementary Fig. 2. The cost-effectiveness acceptability curves (CEACs) showed the probability that physiotherapy added to conventional treatment (CT) is cost effective in comparison to CT only over a range of willingness to pay thresholds. In (a) treatment success is defined as no functional constipation and no laxative use; and in (b) as no functional constipation irrespective of continued laxative use.

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Ethical approval

The Medical Ethical Committee of the University Medical Center Groningen approved this study. All participants gave written informed consent before data collection began.

Trial registration

Netherlands Trial Registry: NTR4797: https://www.trialregister.nl/trial/4654.

Conflict of interest

None declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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