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Differences Between Participants and Nonparticipants in an Exercise Trial for Adults With Rheumatoid Arthritis

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Objective. To investigate the generalizability of the results of a randomized controlled trial on the effectiveness of long-term, high-intensity exercises in the rheumatoid arthritis patients in training (RAPIT) trial by comparing the characteristics of the participants with the nonparticipants.

Methods. Participants and nonparticipants were mailed questionnaires on sociodemographic characteristics, health status, reasons not to participate, and attitudes toward intensive exercise.

Results. The questionnaires from 892 (75%) nonparticipants and 299 (97%) participants were collected. The nonparticipants were slightly older, more often male, and had longer disease duration than the participants. The nonparticipants perceived their disease as more serious, used fewer disease-modifying antirheumatic drugs, had a lower level of education, and a more negative attitude toward intensive exercise.

Conclusion. The results of the RAPIT trial might not be generalizable to the entire target population. To promote participation in long-term, high-intensity exercises, health professionals should more actively discuss the potential benefits of exercise with their RA patients while taking into consideration specific factors related to participation.

INTRODUCTION

The Rheumatoid Arthritis Patients In Training (RAPIT) trial, a large randomized controlled trial on the effectiveness and safety of a long-term, high-intensity weight bearing exercise program in rheumatoid arthritis (RA) patients, confirmed that such programs are effective and safe for most eligible patients (1). It showed positive results in improving physical capacity and functional ability without detrimental effects on disease activity or radiographic damage to the weight-bearing joints. Another finding was an improvement in the emotional status of the patients participating in intensive exercises.

However, before advising a particular RA patient to take part in a long-term, high-intensity weight-bearing exercise program, the clinician or the physical therapist must determine whether this patient differs in a meaningful way from those who participated in the trials in which these programs were investigated. In randomized controlled trials (RCTs), the randomization procedure ensures that the results are unbiased and therefore this study design ensures the internal validity of the study. However, it is widely appreciated that the enrollment process before randomization might be highly selective (2). The eligibility criteria designed to study a relatively homogeneous group of patients might exclude a large fraction of patients, resulting in a highly selected population and limiting the generalizability of the study results (3). In their recently published study on the generalizability of the results of 2 recent clinical trials of anti-tumor necrosis factor α agents to routine care, Sokka and Pincus showed that the generalizability of the conclusions of these major studies might, indeed, be endangered due to eligibility criteria for these trials (4). They demonstrated in 2 patient cohorts (comprising patients from routine-care rheumatology clinics who met the American College of Rheumatology [ACR; formerly American Rheumatism Association] criteria for RA [5] at some time) that most of the patients did not meet the criteria for inclusion in these major clinical trials. The authors concluded that the results of these trials might be valid only in a limited number of RA patients in routine practice.

During the process of recruitment from the potentially eligible patient population (target population), a selection takes place that can endanger the generalizability of the conclusions of the trials to the target population (6). This can be due to physician, patient, or trial-related factors. It is, for example, plausible that eligible patients with more severe disease do not volunteer for the trial and only the patients with better functional status and better prognosis are randomized (7,8). Apart from sociodemographic or disease characteristics, participants might also differ from nonparticipants with respect to health status perception, their attitudes toward exercise, and perceived barriers (9,10). If the differences are significant, the external validity (generalizability) of the study is endangered and the results of the study might not apply to a particular patient, even if he or she fits the eligibility criteria of the original study.

In patients with RA, little is known about recruitment processes before clinical trial randomization or about what motivates a patient to enroll in a trial (4). The aim of the present study was to investigate whether the self-selected group of RA patients that chose to participate in a trial on long-term intensive exercise (RAPIT) differed from the nonparticipants.

SUBJECTS AND METHODS

Subjects.

In June 1997 we initiated the recruitment of participants for the RAPIT trial on the effects of a longterm, high-intensity exercise program in RA patients. To cover the RA population as completely as possible, all available registers of 4 cooperating centers were searched for patients who were, at any point in time, registered with the diagnosis RA, were 20-70 years old, and who had made at least 1 visit to the outpatient department in the past 2 years. Two academic (Leiden University Medical Center and University Hospital of the Free University in Amsterdam) and 2 peripheral (Jan van Breemen Institute in Amsterdam and Leyenburg Hospital in The Hague) rheumatology outpatient departments participated. The clinical records of patients who were, according to the hospital registers, expected to fulfill these criteria were retrieved from the archives. Two investigators (ZdJ and LMJ) screened all available records. The patients were not included in the target population if they did not comply with the age criterion, were not diagnosed with RA, were bedridden, had prostheses of a weight-bearing joint, or were living outside a predefined adherence region of a training or assessment

center. The patients were also excluded if, according to predefined criteria, severe heart, lung, psychiatric, or malignant conditions were present. The patients who were judged eligible after screening the records were named the target population (Table 1).

[TABLE 1]

To avoid preselection of the participants by the treating physician (physician-related factors) (11) and to limit prerandomization losses, the target population patients were approached individually. The target population patients were twice mailed a letter of invitation to participate in the RAPIT study.

Information meetings were organized in Leiden, The Hague, and Amsterdam for the patients who were interested in the RAPIT study. The target population patients who wished to participate in the study (potential participants) were screened in person by one of the investigators (ZdJ, LMJ) for eligibility (Table 2) to confirm that they complied with these criteria (5,12). The eligible patients who agreed to participate and could comply with the training hours (should they be randomized in the training group) were enrolled in the study (participants). The patients who could not be contacted (by mail or, when we got no response, by phone), who declined participation in the process of target population engagement, and who declined participation after screening in person were named nonparticipants. The medical ethics committees in all 4 participating centers approved the study.

[TABLE 2]

Methods.

Within the entire target population, the following characteristics (obtained by the screening the clinical records) were used to compare the participants and the nonparticipants: age, sex, RA duration at the start of the study in years, erosive status (presence of erosions on radiographs of the hands and feet; yes/no), presence of rheumatoid factor (yes/no), number of disease-modifying antirheumatic drugs (DMARDs) used in the past not including the current DMARD (past number of DMARDs). Information on past and present heart or pulmonary comorbidity and medication use of the target population was gathered through clinical records. In addition, potential participants were questioned at the screening visit if they had any cardiovascular or pulmonary complaints, visited a medical specialist because of these complaints in the past, were presently under treatment of a medical specialist, or used medications because of these complaints.

Additional information was gathered through 2 questionnaires: “You and the RA” and “Your Attitude Toward Intensive Exercise.” If the patients did not respond to the first mailing, a second mailing was posted.

By means of the “You and the RA” questionnaire, information was collected on the following items: living status (living alone; yes/no), education level (categorized as low: up to and including lower technical and vocational training; medium: up to and including secondary technical and vocational training; high: up to and including higher technical and vocational training and university), and monthly income per household. Patients were asked to relate, on a 4-point Likert scale, how serious they perceived their illness (in terms of perceived fatigue, morning stiffness, disease activity, and pain). Additional information was obtained regarding visits to an outpatient department or hospitalization due to comorbidity in the 3 months preceding the recruitment procedure, current use of medication due to comorbidity, painkiller use, nonsteroidal anti-inflammatory drug use, and DMARD use. Patients were asked questions about their experience with clinical trials in the past.

Three validated questionnaires were included in the “You and the RA” questionnaire. The Dutch Health Assessment Questionnaire, a measure of functional ability, was derived from the one developed by Fries et al (13) and has been validated for Dutch patients with RA (14). The RAQOL is an RA-specific quality of life questionnaire consisting of 30 items with a yes and no response format (15). It was developed and validated in parallel within the Netherlands and the UK. The EuroQol descriptive components were used. The EuroQol is designed to measure health status and consists of

the EQ-5D self classifier and the EQ-VAS, a visual analog scale on which patients rate their current health state between 0 and 100 (16,17).

Finally, for the nonparticipants who agreed to take part in the postal survey, the questionnaire "You and the RA" included standardized and open questions about reasons not to participate. Examples of statements were given and there was space left for personalized reasons not to participate. The patients were encouraged to choose more than 1 statement if applicable to their situation. The investigators (ZdJ and MM) grouped the reactions into the following categories: transportation problems (e.g., transportation too costly, too complicated), too much time involved, negative disease perception (e.g., RA too severe, too much pain, too little energy), positive disease perception (e.g., in too good shape to need exercise), no wish to be confronted with illness, and the trial setting (e.g., no wish to be randomized, etc).

A second, self-developed questionnaire, "Your Attitudes Toward Intensive Exercise," contained questions about personal attitudes toward intensive exercise. This questionnaire was mailed to the target population patients together with the first letter of invitation for participation and was sent only to patients from Leiden University Medical Centre and Leyenburg Hospital. It was based on the questionnaire used by Gecht et al (18) and consists of 2 statements about the possible positive outcome and 2 statements about the possible negative outcome of a longterm, intensive exercise program. The 4 statements could be answered on a Likert scale with the following items: "fully disagree" (-2), "disagree" (-1), "agree" (1), and "fully agree" (2). A total expectation score (average of 4 statements) was calculated and ranged from -2 (very negative outcome expectation) to -2 (very positive outcome expectation). The questionnaire "Your Attitudes Toward Intensive Exercise" also contained a statement and a question about self efficacy toward long-term, intensive exercise programs and resulted in a self-efficacy score ranging from -4 (low self efficacy) to -4 (high self efficacy). A total outcome expectation score and the self-efficacy score were only calculated if all statements were answered. Internal consistency of the questionnaire "Your Attitudes Toward Intensive Exercise" was tested with Cronbach's alpha and varied from 0.66 to 0.83 (19).

Statistical analysis.

Differences between the participants and nonparticipants were tested with a Mann-Whitney test or chi-square test where appropriate.

RESULTS

A total of 3,273 patient records were available for screening. The 1,537 patients who were found ineligible either did not comply with the residency criterion (40%), had a joint disease other than RA (21%), had a prosthesis of a weight-bearing joint (15%), or were not eligible due to miscellaneous reasons such as severe comorbidity, age, or being in functional class IV (24%).

The trial enrolment process of the target population is shown in Figure 1. The target population consisted of 1,736 RA patients who were judged eligible after screening of the records and were invited to participate in the study. In the process of the target population engagement, 126 patients could not be reached, 1,109 patients declined participation in the trial but cooperated in the postal survey, and 110 patients declined participation and refused to cooperate in the postal survey. At eligibility screening in person, 309 patients were found to be eligible and could be randomized (participants) and 82 eligible patients declined participation but agreed to take the postal survey. In total, the nonparticipant group consisted of 1,427 patients.

[FIGURE 1]

Analysis of data of the entire target population, obtained by screening the clinical records, demonstrated that the nonparticipants (n = 1,427) were slightly older than the participants (n = 309); median age (interquartile range [IQR]) was 57 (16) years versus 54 (16) years; $P = 0.001$. Nonparticipants were more often male: 28% versus 21%; $P = 0.021$). Nonparticipants had a longer duration of RA: median (IQR) of 7 (9) years versus 6 (9) years; $P = 0.002$. No significant differences

were found with regard to the presence of rheumatoid factor, erosion status, or past number of DMARDs.

The questionnaire "You and the RA" was mailed to 1,500 RA patients; 309 participants and 1,191 nonparticipants. The nonparticipants who could not be contacted (n = 126) and those who declined participation and refused to cooperate on the postal survey (n = 110) were not sent a questionnaire.

After 2 mailings, 82% (972 of 1,191) of the nonparticipants and 97% (299 of 309) of the participants returned the questionnaire. A total of 1,271 questionnaires were returned (80 nonparticipants returned the questionnaire blank), yielding an 85% crude response rate. Finally, the data from questionnaires of 299 participants (10 questionnaires not returned) and 892 nonparticipants (219 questionnaires not returned, 80 returned blank) were available for evaluation. These data, which were used for the final evaluation, are presented in Tables 3 and 4 and represent 69% of the target population. The data on the diseaserelated and sociodemographic characteristics of the nonparticipants and participants in the RAPIT study who returned the completed questionnaire confirm the differences in age, sex, and RA duration found in the entire target population and are presented in Table 3. The nonparticipants were significantly older, more often male, and had longer RA duration then the participants. Moreover, the level of education of the nonparticipants was significantly lower than that of the participants, although there was no difference in monthly household income. The nonparticipants did not significantly differ from the participants as far as the present and past cardiovascular and pulmonary comorbidity was concerned (6.5% versus 5.8%, $P = 0.782$ and 6.6% versus 4.7%; $P = 0.326$, respectively). This was also reflected in the comedication presently used for cardiovascular or pulmonary comorbidity (21.8% versus 19.8%; $P = 0.512$ and 5.5% versus 3.4%, $P = 0.164$, respectively). However, recent comorbidity, reflected in the number of patients who visited an outpatient department or required hospitalization due to causes other than RA in the past 3 months, differed significantly between nonparticipants and participants (37.7% versus 13.9%; $P = 0.001$ and 12.4% versus 5.4%; $P = 0.001$, respectively).

[TABLE 3 AND 4]

The data on clinical health status—expressed as perceived fatigue, morning stiffness, disease activity, pain, current medication use due to RA, functional status, quality of life, and utility—of the nonparticipants and participants who completed the questionnaire are presented in Table 4. The nonparticipants perceived that in the 3 months preceding recruitment they had more RA disease activity, more morning stiffness, and they used less DMARDs than the participants. Except for perceived RA disease activity, morning stiffness, and current use of DMARDs, there were no differences between the groups.

The questionnaire "Your Attitudes Toward Intensive Exercise" was mailed to 807 target population patients; 624 patients (149 participants and 475 nonparticipants) returned their questionnaire completed (82%). The outcome expectations with respect to a long-term intensive exercise program were significantly less positive in the nonparticipants than in the participants. The median (IQR) outcome expectation scores amounted to 0.25 (-1.0, 1.0) for nonparticipants and 1 (0.5, 1.5) for participants ($P = 0.002$). The self-efficacy score (median [IQR]) was lower in nonparticipants than in participants and amounted to 0 (-1, 2) and 2 (0, 3), respectively ($P = 0.001$).

We found that 36.8% of the nonparticipants and 38.9% of the participants had participated in a clinical trial in the past and rated this as a positive experience in most cases (76.4% versus 77.4%; $P = 0.752$). More than 68% of the nonparticipants who completed the questionnaire stated more than 1 reason for their decision not to participate. The following reasons were mentioned: transportation problems (23%), time involved (30%), negative disease perception (16%), positive disease perception (21%), and no wish to be confronted with illness (31%). Twenty-four percent of the nonparticipants did not wish to participate because of reasons related to the trial design.

DISCUSSION

In a study situation, long-term, high-intensity exercise programs have beneficial effects for RA patients (1,20 -23). We addressed the question of generalizability of the results of the recently

performed RAPIT trial and investigated which factors motivated the patients to participate or not. The present study demonstrates that the nonparticipants differed significantly from the participants in a number of characteristics: sociodemographics (age and sex), disease specifics (RA duration, current use of DMARDs), disease perceptions (perception of pain and morning stiffness), outcome expectations, and self efficacy. The nonparticipants had more outpatient visits shortly prior to the start of the recruitment procedure or were more often hospitalized for reasons unrelated to RA. The expected practical problems and perceived disease severity (too good or too bad for exercise) were the most frequently reported barriers to participation.

To our knowledge, no research on the generalizability of a high-intensity exercise program for RA patients or on the determinants of their participation in such a program has yet been published. The subject of generalizability does not get much attention in clinical research. Gross et al reviewed 172 RCTs published in major medical journals that involved individual people as the unit of randomization (2). They conclude that only 74 (43%) reported the number of persons who were actually eligible for participation "making it difficult for readers to gauge the extent to which the participants may represent a highly selected subgroup." It is, however, an important issue because the participating patients can differ significantly from nonparticipants in characteristics important to the effectiveness of the treatment under investigation and to its implementation (24,25).

A survey of the literature available did show that participants in fitness programs, rehabilitation programs, and clinical trials are often a selected group of people. They are younger (26), have a lower risk for adverse events (27,28), and have fewer functional impairments (6) than the nonparticipants. They tend to evaluate their health more favorably than nonparticipants (8). Our findings that the RA patients participating in the RAPIT study tended to be patients with more favorable disease characteristics and a higher level of education are consistent with these studies.

When advising an individual RA patient to participate in a long-term, high-intensity exercise program, the eligibility criteria applied in the RAPIT trial must be kept in mind. Besides the age criterion, the exclusion from trial participation of patients with prostheses of weight-bearing joints, ACR functional class IV, or serious internal or psychiatric diseases is of most significance. This implies that the conclusions of the trial cannot simply be extended to patients with severe physical or functional limitations.

Considering the generalizability of the results of the study on the effectiveness and safety of long-term, highintensity exercises to the target population, we do not expect the differences in sex and age between the participants and the nonparticipants large enough to be of clinical relevance. Others have already demonstrated that elderly patients are significantly able to improve their physical fitness (28). In fact, patients with active RA are also able to improve in physical fitness through intensive exercises (29). However, the fact that the nonparticipants used fewer DMARDs, had a lower level of education, and had a more negative self perception of the severity of their RA might signal an important issue. Socioeconomic status is an issue in health politics because lower socioeconomic status has repeatedly been reported to be associated with worse disease outcome, lower compliance to medical treatment, and higher mortality (30,31). Negative illness perceptions can also negatively contribute to health outcome in patients with RA (32). We can therefore speculate that people who adhere less well to medical treatment, such as taking a DMARD, and have a more negative perception of disease severity are patients with the worst prognosis and are less easily motivated to participate in, and adhere to, intensive exercises. This might be a group to which the results of the RAPIT trial are not generalizable. The fact that the nonparticipants visited an outpatient department more often than participants or were more often admitted prior to recruitment could have an influence on the decision to participate or not.

The purity and representativeness of our data can be questioned on several grounds. The data were obtained by means of a postal survey and thus represent only about two-thirds of the target population (questionnaires of only 299 [97%] participants and 892 [75%] nonparticipants were available for evaluation). In addition, the data on nonparticipants who could not be contacted (n = 126) and nonparticipants who declined to cooperate in the postal survey (n = 110), which represents 14% of the target population, was limited. Selective nonresponse might play a role.

However, our response rate is comparable with other studies and is considered satisfactory (33,34). The investigation of a nonresponse phenomenon in postal surveys has been studied in the Dutch

population and did not reveal any significant indication for selective nonresponse (33). In our study, the comparison of the results obtained by analysis of the data of the entire target population (result of screening of the clinical records) suggests that information provided by means of postal survey might be extended to the entire target population.

The lesson from our study is the following: the individual's perception of disease severity, outcome expectations, and perception of self efficacy seem to be important factors in the decision making for participation in this trial. Because practical issues (such as time spent on the exercise program and the associated costs) were reported by the nonparticipants as at least one of the reasons not to participate, we would advise anticipating these problems in the process of implementation of the long-term, intensive exercise program to increase motivation to participate. When health professionals wish to increase the participation rate of RA patients (especially men, older patients, those with the worst perception of their illness, and those with a lower level of education), they should initiate exercise discussions with those patients, teach them the values of exercise, its potential benefits, and how to adopt and maintain an exercise routine (10).

We propose that future research should be directed toward the effectiveness and compliance of intensive exercise in daily practice in extended patient populations.

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TABLES

Table 1. Trial recruitment terminology

Term	Definition
Target population	Patient population judged eligible after screening of the available clinical records and to whom the trial's results are expected to apply.
Potential participants	Proportion of target population who was contacted and underwent eligibility screening in person.
Nonparticipants	Proportion of target population who could not be contacted or who declined participation either in the process of target population engagement or after eligibility screening in person.
Participants	Proportion of potential participants who were found eligible after eligibility screening in person and were randomized.

Table 2. Inclusion criteria of RAPIT trial*

Age 20–70 years
RA according to ACR criteria 1987 (5)
ACR functional class I–III (12)
Stable DMARD in past 3 months
Able to cycle
Willing to exercise biweekly on fixed schedule
Living within a predefined adherence region of training or assessment center
No prosthesis of a weight-bearing joint
No cardiopulmonary disease excluding intensive exercise
No comorbidity causing a shortened life expectancy
No serious psychiatric disease

RAPIT = Rheumatoid Arthritis Patients in Training; RA = rheumatoid arthritis; ACR = American College of Rheumatology (formerly American Rheumatism Association); DMARD = disease-modifying antirheumatic drug.

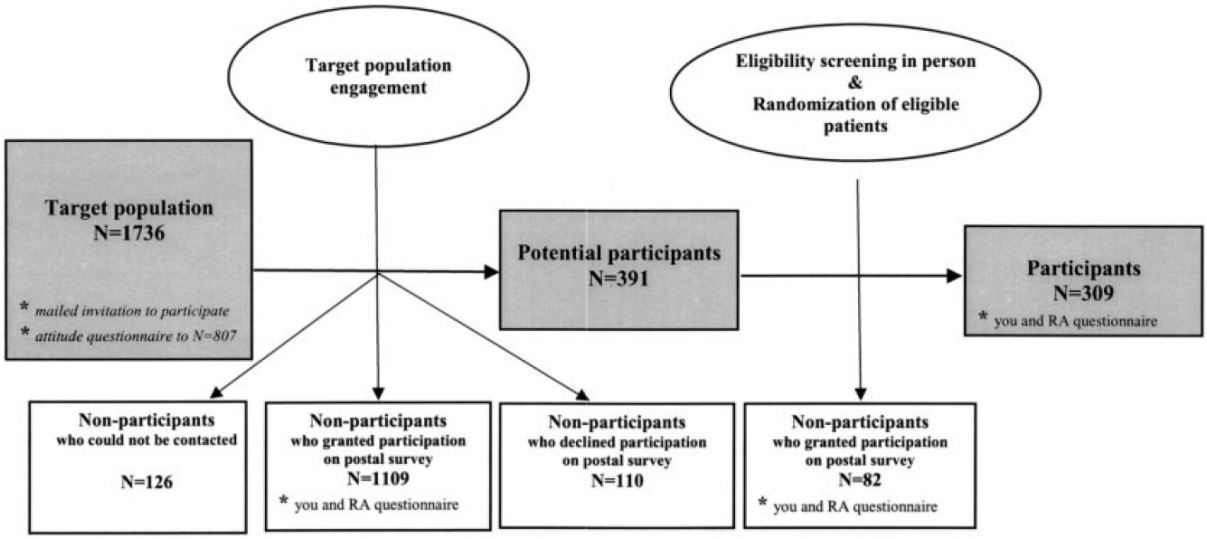

Figure 1. The trial enrollment process. RA = rheumatoid arthritis.

Table 3. Disease-related and sociodemographic characteristics of the participants and nonparticipants in the RAPIT study who returned the completed questionnaire*

Characteristic	Participants (n = 299)	Nonparticipants (n = 892)
Age, median (IQR) years	54 (45–61)	57 (48–64)†
Female, no. (%)	236 (79)	636 (71)†
RA duration, median (IRQ) years	6 (3–12)	8 (4–14)†
RF positive, no. (%)	210 (70)	646 (72)
Erosive status, no. (%)	221 (74)	665 (75)
Past number of DMARDs, median (IQR)	2 (1–2)	2 (1–3)
Living alone, no. (%)	65 (22)	179 (20)
Education level		
Low, no. (%)	106 (35)	411 (46)†
Medium, no. (%)	108 (36)	240 (27)
High, no. (%)	80 (27)	208 (23)
Income per household/month		
<$600 US, no. (%)	24 (8)	67 (7)
$600–800 US, no. (%)	38 (13)	125 (14)
$800–1,600 US, no. (%)	105 (35)	315 (35)
$1,600–2,400 US, no. (%)	55 (18)	155 (17)
$>2,400 US, no. (%)	30 (10)	91 (10)

* Erosive status = presence of erosions on the radiographs of the hands and feet. Past number of DMARDs = number of DMARDs used in the past except the current DMARD. Educational level: low = up to and including lower technical and vocational training; medium = up to and including secondary technical and vocational training; high = up to and including higher technical and vocational training and university. RAPIT = Rheumatoid Arthritis Patients in Training; IQR = interquartile range; RA = rheumatoid arthritis; RF = rheumatoid factor; DMARD = disease-modifying antirheumatic drug.
† $P = 0.005$. Differences were examined by using chi-square or Mann-Whitney U test where appropriate.

Table 4. Current clinical health status, functional status, quality of life, and utility of participants and nonparticipants in RAPIT study who returned the completed questionnaire*

	Participants (n = 299)	Nonparticipants (n = 892)
Current clinical health status		
RA disease activity, Likert scale 0–4, mean ± SD	2.7 ± 0.9	3.0 ± 1†
Morning stiffness, Likert scale 0–4, mean ± SD	2.5 ± 1.0	2.7 ± 1.0†
Fatigue, Likert scale 0–4, mean ± SD	2.8 ± 1.1	2.8 ± 1.0
Pain, Likert scale 0–4, mean ± SD	2.8 ± 0.9	2.9 ± 1.0
Current use of painkillers, no. (%)	57 (19)	196 (22)
Current use of NSAID, no. (%)	212 (71)	660 (74)
Current use of DMARD, no. (%)	251 (84)	651 (73)†
Functional status		
HAQ score, 0–3, median (IQR)	0.75 (0.25–1.14)	0.75 (0.25–1.25)
Quality of life		
RAQOL, 0–30, median (IQR)	11 (6–17)	10 (5–17)
Utility		
EQ-5D, median (IQR)	0.69 (0.59–0.73)	0.69 (0.59–0.76)
EQ-VAS, 0–100, median (IQR)	70 (55–80)	70 (55–80)

* RAPIT = Rheumatoid Arthritis Patients in Training; RA = rheumatoid arthritis; NSAID = nonsteroidal antiinflammatory drug; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessement Questionnaire; IQR = interquartile range; RAQOL = Rheumatoid Arthritis Quality of Life questionnaire; EQ-5D = EuroQol self classifier; EQ-VAS = EuroQol visual analog scale.
† $P = 0.001$. Differences were examined by using chi-square or Mann-Whitney U test where appropriate.

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