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Continued participation in a ten-year tight control treat-to-target study in rheumatoid arthritis: why keep patients doing their BeSt?

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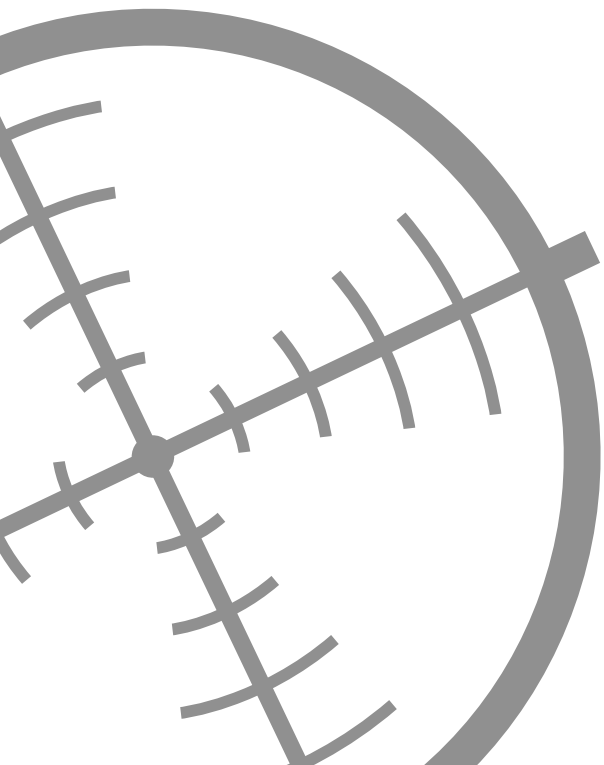

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ABSTRACT

Objective

To identify risk factors for early study termination and motivators for adherence to a long-term follow-up trial and to improve completeness of long-term studies.

Methods

Risk factors for early termination in 508 included patients were identified through Cox regression analysis. Patients completing the 10-year follow-up filled in a questionnaire on possible motives for continued study participation.

Results

Risk factors for early termination were higher age (hazard ratio [HR] 1.03, 95% confidence interval [95% CI] 1.02 – 1.04), functional disability during the preceding year (HR 1.54, 95% CI 1.20 – 1.99), having achieved drug-free remission (HR 6.62, 95% CI 2.07 – 21.14), limited joint damage (HR 0.98, 95% CI 0.97 – 0.995 for actual damage; HR 0.83, 95% CI 0.73 – 0.94 for damage progression), and few adverse events (HR 0.35, 95% CI 0.26 – 0.47). A total of 288 of 313 patients (92%) attending the last visit answered the questionnaire. The majority mentioned contributing to scientific research (97% agreed), helping other patients (91%), and learning about new treatment strategies (84%) and their disease (85%) as reasons to continue participation. Next, patients mentioned tight control (202 of 278 patients), good treatment strategy (128 of 278), good medication (117 of 278), and good half-term results (102 of 278) as motivators. More than 95% of patients experienced participation "as expected" or "better than expected." Additional examinations during yearly visits (extra questionnaires, imaging) were mentioned as "worse than expected" (10%), as was answering routine questionnaires (7%).

Conclusion

Continued participation was relatively high in the Treatment Strategies for Rheumatoid Arthritis (BeSt) study. Higher age, functional disability, drug-free remission, little joint damage, and few adverse events predicted early study termination. Main motives for continued participation were a willingness to contribute to research, help future patients, and because patients had good experiences with the study protocol.

INTRODUCTION

Clinical trials with long follow-up duration can provide data on the long-term outcomes of interventions under study, late side effects, or rare events. It is sometimes challenging to motivate patients to continue participation in such trials, as shown by varying completeness percentages that are reported in randomized clinical trials with a 10-year follow-up, ranging from 96% to only 43%.[1–8] Continued participation may depend on the burden and content of scheduled study visits, type of disease, and the results of study intervention, as well as on the care and motivational efforts from the study team. We set out to investigate the motives of patients who completed the BeSt (Dutch acronym for Treatment Strategies for Rheumatoid Arthritis) trial, a 10-year follow-up study evaluating four dynamic treatment strategies in patients with early rheumatoid arthritis (RA). In this study, visits every three months and a treat-to-target strategy based on a dynamic treatment protocol with established antirheumatic medication were continued during the total follow-up period. At every visit, a physical examination was performed by a study nurse, as were laboratory tests, and multiple questionnaires were completed. At yearly intervals, radiographs and joint imaging with other techniques were obtained.

The aim of this study was to identify predictors (including both patient and clinical characteristics) of early study termination. In addition, motives for patients' adherence were examined in order to identify issues that may be targeted in future long-term follow-up trials to improve compliance.

PATIENTS AND METHODS

Study design

The BeSt study was a multicenter, randomized, single-blind clinical trial set up to evaluate four dynamic treatment strategies in 508 patients with recent-onset active RA (1987 American College of Rheumatology classification criteria).[9] Details of the study have been previously described.[10] All patients gave written informed consent for the original study, and after separate approval from the medical ethics committees of the participating centers, also gave written informed consent for the additional questionnaire concerning the present topic.

Patients were randomized to sequential monotherapy, step-up combination therapy (both starting with methotrexate monotherapy), initial combination with methotrexate, sulphasalazine, and prednisone, or initial combination with methotrexate and infliximab. Following a treat-to-target strategy in all four arms, treatment adjustments were made based on Disease Activity Score (DAS) assessments, measured at visits every three months.[11] When disease activity was high (DAS >2.4), the next treatment step was taken. If low disease activity (DAS ≤2.4) was maintained for at least 6 months, medication was tapered to a maintenance dose. In case of longstanding remission (DAS <1.6),[12] medication was discontinued. As soon as disease activity increased to DAS >2.4, medication was restarted.

Study end points

To detect predictors for early study termination, a univariable Cox regression analysis was performed, including all 508 patients. Determinants entered in the model were age, sex, randomization arm, level of education, and clinical characteristics as present in the year preceding the end point; functional ability (measured with the health assessment questionnaire [HAQ], range 0 – 3);[13] the trend of functional ability (i.e., increasing or decreasing HAQ), disease activity measured with the DAS;[11] radiographic joint damage (measured with the Sharp/van der Heijde score [SHS], range 0 – 448);[14] SHS progression; the occurrence of a serious adverse event (SAE); the number of SAEs; the number of AEs; and the presence of drug-free remission (DAS >1.6 after cessation of antirheumatic medication). Determinants measured at baseline were entered in the model as regular variables, and determinants measured during follow-up were entered as time-dependent variables. Predictors with a p value less than 0.10 were entered in a multivariable Cox regression analysis, where a p value less than 0.05 was considered statistically significant.

At the final visit, patients filled in an extensive questionnaire about their motivation to continue participation, their opinion about study-related and care-related matters, and their feelings with regard to accomplishment of follow-up. The questionnaire was used in order to identify factors that motivate and demotivate continued study participation. As this is a relatively novel area in medicine, no validated questionnaires have been developed. Therefore, this questionnaire was composed by our study team with questions derived from other surveys,[15,16] then completed with new questions. To encourage patients to answer all questions, mostly closed questions were asked. To assure that questions were clearly formulated and did not take too much time to answer, a pilot study with 5 patients at the outpatient clinic of the Leiden University Medical Center was performed.

The questionnaire was constructed as follows: to investigate potential motivators for patients to remain in the study, the first part of the questionnaire asked patients whether they (dis) agreed on a 4-point Likert scale (fully agree, partially agree, partially disagree, and fully disagree) with 19 statements on possible reasons to continue participation. In addition, using 1 question with 10 options (patients could mark more than 1 answer), patients were asked why they continued study participation.

Patients were then asked how they experienced specific study-related matters, e.g., study visits, targeted treatment, and filling in questionnaires, as well as care-related matters, e.g., care by the rheumatologist and care by the research nurse. Answer options were much better than expected, slightly better than expected, conform to expectations, I had no expectations, slightly worse than expected, and much worse than expected.

Subsequently, 4 closed questions (yes/no) inventoried feelings about completing the BeSt study. One question with 7 options asked once more about the feelings of the patient (patients could mark more than 1 answer).

During the course of the study, newsletters (1 or 2 per year) were sent to the patients, and 3 meetings for study participants were organized where published study results were presented

by the study physicians. The results were also recorded in booklets, which were shown to all patients present at the meetings and sent to patients who did not attend. We asked patients' opinion about these matters in 12 questions (5 multiple choice questions and 7 questions with several options, where patients could mark more than 1 answer).

Statistical analysis

Descriptive statistics were used to describe demographic and clinical characteristics of the patients, as well as answers on relevant questions in the questionnaire at year 10. Answers to the questionnaire were summarized as follows: numbers and percentages of answers given were noted in cases of multiple choice questions with only 1 possible answer, and numbers only in cases of questions with more than 1 possible answer.

RESULTS

After 10 years, 307 of 508 included patients (60%) were still under follow-up, while 201 had dropped out (reasons: 76 patient refusal, 9 revised diagnosis, 35 comorbidity, 39 deceased, and 42 other/unknown). Of the patients who dropped out, 6 responded to our recall and agreed to fill in the additional questionnaire at year 10. Of the 307 patients under follow-up, 282 filled in the questionnaire. Together with 6 patients responding to the recall, this brings the total to 288 of the original 508 (57%), or 92% of the 313 patients who showed up for the final visit (307 completers and 6 dropouts that responded to the recall). Demographic and clinical characteristics of these patients are summarized in Table 1.

Table 1. Demographic characteristics at year 10.

Characteristics	Questionnaire filled in n=288	Questionnaire not filled in n=220
Age (years), mean (SD)	61 (12)	68 (15)
Female, n (%)	194 (67)	149 (68)
HAQ, mean (SD)	0.6 (0.6)	*NA*
DAS <1.6, n (%)	144 (53)	*NA*
DAS 1.6 – 2.4, n (%)	77 (28)	*NA*
DAS >2.4, n (%)	52 (19)	*NA*
Treatment strategy, n (%)		
Sequential monotherapy	74 (26)	52 (24)
Step-up combination therapy	60 (21)	61 (28)
Initial combination with prednisone	73 (25)	60 (28)
Initial combination with infliximab	81 (28)	47 (21)
Current methotrexate use, n (%)	163 (57)	*NA*
Current infliximab use, n (%)	52 (18)	*NA*
Current prednisone use, n (%)	25 (9)	*NA*
Current drug-free remission, n (%)	45 (16)	*NA*

DAS, disease activity score (<1.6 denoted clinical remission, 1.6 – 2.4 denotes low disease activity and >2.4 denoted high disease activity); HAQ, health assessment questionnaire (range 0 – 3); NA, not available, as these patients were not under follow-up.

Risk factors for early study termination

Univariable Cox regression analysis revealed as follows the potential risk factors for premature study discontinuation in the subsequent year: higher age, randomization arm, DAS, functional disability, drug-free remission, joint damage, joint damage progression, occurrence of an SAE (yes/no), and the number of SAEs and AEs. In the multivariable Cox regression analysis, a higher age (hazard ratio [HR] 1.03), functional disability (measured with the HAQ; HR 1.54), and having achieved drug-free remission (HR 6.62) were independent predictors for study discontinuation in the subsequent year (Table 2). The more AEs a patient had reported, the lower the risk of dropping out (HR 0.35). This was also true for patients with less joint damage (measured with the SHS; HR 0.98) and less joint damage progression (measured as ΔSHS; HR 0.83) (Table 2).

Table 2. Results from the multivariable Cox regression analysis with early study termination as outcome.

	HR	**95% CI**
Age (years)	1.03	1.02 – 1.04
Treatment strategy		
Sequential monotherapy	1.39	0.90 – 2.14
Step-up combination therapy	1.48	0.95 – 2.28
Initial combination with prednisone	1.29	0.83 – 1.99
Initial combination with infliximab	*ref*	*ref*
Mean DAS*	1.10	0.90 – 1.35
Mean HAQ*	1.54	1.20 – 1.99
DFR*	6.62	2.07 – 21.14
SHS*	0.98	0.97 – 0.995
SHS progression*	0.83	0.73 – 0.94
Number of AE*	0.35	0.26 – 0.47
Occurrence of SAE (yes/no)*	1.59	0.74 – 3.43
Number of SAE*	1.73	0.99 – 3.03

*During the preceding year of follow-up

95% CI, 95% confidence interval; AE, adverse event; DAS, disease activity score; DFR, drug-free remission; HAQ, health assessment questionnaire; HR, hazard ratio; SAE, serious adverse event; SHS, Sharp/ van der Heijde score.

Motivators for continued study participation

The questionnaire started with 19 statements on possible reasons to continue study participation. Patients most agreed with the following reasons for continuation of study participation: to contribute to scientific research (77% fully agreed, 20% partially agreed), to help other patients (61% fully agreed, 30% partially agreed), "I have nothing to lose" (52% fully agreed, 28% partially agreed), faith in the hospital and its employees (52% fully agreed, 24% partially agreed), to gain understanding of new treatment strategies (50% fully agreed, 34% partially agreed), and to gain understanding of the disease (43% fully agreed, 42% partially agreed). Patients least often agreed with the statements that proposed social contact as a reason for continued participation, a sense of "being part of something," and

a sense of obligation toward their rheumatologist to continue participation in the BeSt trial. Figure 1 represents the responses to all statements. Comparing all answers between treatment strategies suggested only 1 difference; 42% and 41% of patients in arm 1 and 2 (both starting with methotrexate monotherapy), respectively, stated that a better treatment was a motivator to continue study participation, compared to 63% and 61% in arm 3 and 4, respectively (both starting with combination therapy).

Next, the patients were asked to mark 1 or more possible reasons why they continued participation. In total, 278 patients marked 912 reasons (median 3 per person) as follows: tight disease monitoring (202 times), contribution to scientific research (176 times), good treatment strategy (128 times), good medication (117 times), favorable half-term study results (102 times), and a good relation with the nurse (97 times). Fewer patients marked low disease activity (48 times), high disease activity (26 times), to please the treating physician (7 times), and other (9 times).

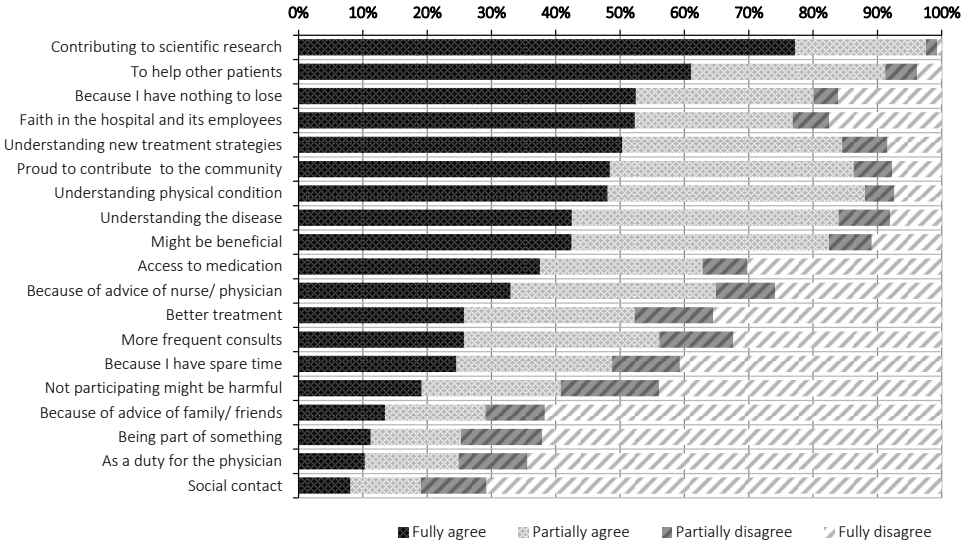

Figure 1. Answers (percentage of patients) to the statements about continuing study participation on a 4-point Likert scale.

Experiences with study-related and care-related issues

Patients were asked how they experienced study-related and treatment-related concepts. To all matters, the majority of patients answered that their experience had conformed to expectations or was better than expected. In particular, patients were positive about the care as provided by the research nurse (40 – 50% of patients answered that how the nurse listened, answered questions, and performed the examinations was much better than expected, and an additional 15 – 20% answered that this was slightly better than expected).

Ten percent of patients reported that the additional yearly examinations, i.e., dual-energy x-ray absorptiometry, radiographs of hands and feet, and extra questionnaires, and the time these examinations took, were worse than expected. Also, 7% of the patients reported the questionnaires (number, length, and difficulty of wording) were worse than expected. A complete overview of all answers is shown in Figure 2.

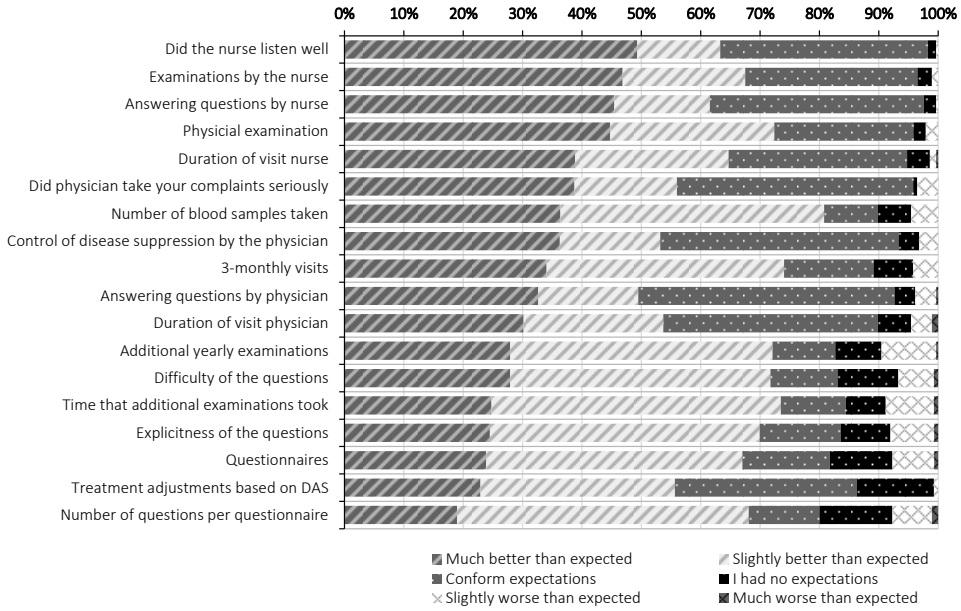

Figure 2. Answers (percentage of patients) to the experience of study-related and care-related matters. DAS, disease activity score.

Feelings

Almost all patients were happy (97%), satisfied (99%), and proud (71%) at the moment of completing follow-up, and only 2 patients (0.7%) regretted participating. When patients were asked to mark 1 or more feelings, 20 patients also marked the feeling of relief at the end of the study. Disappointment was marked by 45 patients and fear by 7 patients. Finally, after completing the 10-year follow-up of the BeSt study, 74% of the patients reported they would again participate in a trial, and 94% would recommend participation in a trial to friends or family members.

Drop outs responding to the recall

Six patients who had dropped out and responded to the recall gave the following answers: 4 of the 6 patients fully agreed with the statement that contribution to scientific research is an important motivator, and 4 patients fully agreed with the statement about the relevance

of helping future patients. Five of the patients fully disagreed with the statement that they had nothing to lose. Answers about treatment-related or care-related matters were not obviously different from patients that completed the total follow-up. None of the patients regretted participation, and all were happy and satisfied that they had participated; however, 4 patients stated that they would not participate in a future trial. Despite this, 4 patients would recommend study participation to friends and family.

Informing patients about the study results

Concerning questions regarding the newsletters, 283 patients marked 370 answers, mostly stating that they found the newsletters informative (207 times) and interesting (138 times; and 25 other answers). Also, 90% of the patients reported that the frequency of the newsletters was sufficient. Seventy percent of the responding patients had attended 1 or more meetings. Regarding the meetings, 103 patients gave 254 answers, reporting that they found them informative (75 times), well organized (70 times), and interesting (69 times; and 40 other answers). Eighty eight percent of the patients said the frequency of these conferences was sufficient. The booklets with published study results were found to be informative (210 times) and interesting (132 times; out of 373 answers by 279 patients; 31 other answers).

DISCUSSION

In long-term follow-up studies, motivating patients to continue participation might be challenging. Patient dropouts are undesirable as it may bias long-term results due to selective dropout. Identifying why patients become lost to follow-up, or reversely, why patients continue study participation, may provide motivators for future study participants. We therefore identified risk factors for premature trial discontinuation of patients in the BeSt study, and assessed motivators and experiences among patients who did complete the 10-year follow-up.

Several predictors of dropping out were identified. Older patients were more likely to leave the study, as were patients with a worse functional ability, regardless of age. Patients with more absolute radiographic joint damage and damage progression more often continued study participation. This might be explained by self-interest of these patients and by maintaining the opportunity of treatment intensification every 3 months as dictated by the study protocol. Reporting more AEs was also correlated with study continuation, in which case patients might be more aware of the need of strict monitoring. Contrary to our expectations, disease activity in itself was not a predictor for premature discontinuation, but having achieved drug-free remission was. It is imaginable that patients in (longstanding) drug-free remission no longer feel a personal benefit from continued participation in the study. Reisine *et al* found that psychosocial and socioeconomic factors, and also having fewer joint groups with flares, were associated with continued study participation, rather than other clinical features.[17]

The main reasons for patients to continue study participation were a willingness to contribute to scientific research and the society, to help future patients, to gain understanding in their

disease and the treatment strategies, and a sense of "having nothing to lose." Altruistic motives are also known motivators to enter a clinical study,[18–20] although a study from Romania revealed payment and free complete blood tests as motivators to participate.[15] We aimed to increase the sense of contribution to science by presenting the study results through newsletters, booklets, and meetings for trial participants. We expected that the continued intensive follow-up program (lasting between 15 and 60 minutes per visit) might be a reason to discontinue participation. However, the opposite might be true, since many patients reported "good monitoring" as a reason for continued participation. This confirms the finding of Strusberg *et al*.[21]

In addition to frequent monitoring as a reason for continued participation, patients were mostly positive about their experiences with study-related and treatment-related matters. They were especially satisfied about visiting the study nurses, and finding attention, time investment, and 2-way communication beyond their expectations. We suggest that trained and dedicated nurses should be employed to motivate patients to continue in a long-term study. Conversely, as patients reported disappointment about the questionnaires (difficulty of the questions, time), future studies should aim to minimize using questionnaires, or consider "proxy-ratings," i.e., a partner or relative of the patient answers the questionnaire from the patient's point of view. Also, yearly additional examinations and tests were negatively mentioned and could be avoided in future trials. However, particularly for long-term follow-up studies, repeated measurements may be important and unavoidable. Therefore, we suggest thoroughly informing the patients about the scientific background and value of such examinations. Despite this, most patients are satisfied and do not regret their contribution. This is also reflected by most patients responding that they would again participate in a trial (74%) and would recommend participation to friends and family (94%), which appears to reflect a wish that others now may contribute to science.

Considering the continued high frequency of study visits and the reported burden of questionnaires and additional examinations, we consider a 60% completion rate after 10 years of continued follow-up a success. Other 10-year follow-up studies in various areas of medicine have reported completion rates of 43–96%.[1–8] Rates partially depend on the study design and on whether deceased patients are calculated as dropouts or as completers. Most 10-year follow-up studies report data of relatively rare study visits or even a single observation at year 10 after an intervention at baseline. This requires less commitment from patients compared to the continued visits (every 3 months) required in the BeSt study. The type of disease under study could also influence continued participation, as patients with a severe or life-threatening disease might be more dedicated to remain in touch or can be recalled.

Two other intervention studies in RA have reported long-term follow-up results. In the FINRACo (Finnish Rheumatoid Arthritis Combination Therapy) trial treatment was targeted at remission during 5 years.[22] After 11 years, 138 of 195 randomized patients (71%) responded to the recall. In the COBRA (Combinatietherapie bij Reumatoïde Artritis) study, 155 patients were treated by protocol during 56 weeks and were also recalled after 11 years.[23] Forty-one

patients (26%) were lost to follow-up and 20 patients (13%) refused full participation. A recall design might result in a higher percentage of patients providing data at the final study visit, at the expense of information over time, and with the risk of a non-representative part of the study population responding to the call.

In conclusion, continued participation in the BeSt study was relatively high. Predictors for early termination were functional disability, higher age, achieving drug-free remission, and experiencing limited joint damage (progression) and few adverse events. The high completion rate may be related to motivators such as a wish to contribute to science, learn more about an illness and its treatment, the personal benefit of study-associated monitoring visits, the effect of available therapies, and a good rapport with the study nurse. By cultivating these motivators, premature discontinuation in long-term follow-up studies may be avoided or reduced.

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