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The effect of prophylactic calcium and magnesium infusions on the incidence of neurotoxicity and clinical outcome of oxaliplatin-based systemic treatment in advanced colorectal cancer patients ☆

N. Knijn [a,b], J. Tol [a], M. Koopman [c], M.J.B.P. Werter [d], A.L.T. Imholz [e], F.A.A. Valster [f], L. Mol [g], A.D. Vincent [h], S. Teerenstra [i], C.J.A. Punt [a,*]

[a] Department of Medical Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[b] Department of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[c] Department of Medical Oncology, University Medical Centre Utrecht, Utrecht, The Netherlands
[d] Department of Internal Medicine, VieCuri Hospital, Venlo, The Netherlands
[e] Department of Internal Medicine, Deventer Hospital, Deventer, The Netherlands
[f] Department of Internal Medicine, Hospital Lievensberg, Bergen op Zoom, The Netherlands
[g] Comprehensive Cancer Center East (IKO), Nijmegen, The Netherlands
[h] Department of Biometrics, Netherlands Cancer Institute, Amsterdam, The Netherlands
[i] Department of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

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ABSTRACT

Background: Peripheral sensory neurotoxicity is a frequent and potentially debilitating side effect of oxaliplatin treatment. Calcium and magnesium (Ca/Mg) infusions are frequently used to prevent this toxicity. However, concerns about a negative impact of Ca/Mg infusions on outcome have been raised. We retrospectively assessed the effect of Ca/Mg infusions on the incidence of neurotoxicity and on clinical outcome in advanced colorectal cancer (ACC) patients treated in the phase III CAIRO2 study.

Materials and methods: Seven hundred and fifty five previously untreated ACC patients were randomised between treatment with capecitabine, oxaliplatin and bevacizumab or the same combination with the addition of cetuximab. Patients were retrospectively divided into two groups: patients in the Ca/Mg^{+} group received Ca/Mg at least during their first treatment cycle, and patients in the Ca/Mg^{-} group did not.

Results: Seven hundred and thirty two patients were evaluable for this analysis. The Ca/Mg^{+} group consisted of 551 patients, the Ca/Mg^{-} group consisted of 181 patients. The incidence of all grade neurotoxicity in the Ca/Mg^{+} group and the Ca/Mg^{-} group was 85% and 92%, respectively ($p = 0.02$), and the incidence of grade $\geqslant 2$ neurotoxicity was 40% and 45%, respectively ($p = 0.22$). The median PFS in the Ca/Mg^{+} versus Ca/Mg^{-} group was 10.1 versus 10.7 months ($p = 0.92$), the median OS was 19.8 versus 20.7 months ($p = 0.10$), and the response rate was 43.1% versus 50% ($p = 0.11$), respectively.

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* *Corresponding author:* Address: Department of Medical Oncology, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 24 3613457; fax: +31 24 3540788.
E-mail address: C.Punt@onco.umcn.nl (C.J.A. Punt).

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Conclusions: In this largest retrospective analysis to date we observed that Ca/Mg infusions significantly reduced all grade oxaliplatin-related neurotoxicity. Ca/Mg infusions did not affect the clinical efficacy of treatment.

1. Introduction

Palliative systemic treatment has shown a clinically relevant survival benefit in patients with advanced colorectal cancer.[1] Currently available cytotoxic drugs are the fluoropyrimidines, irinotecan and oxaliplatin. Our group and others previously have shown that these drugs may be used either sequentially or in combination.[2,3] Drugs targeting the vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR) have further improved the prognosis of these patients.[4] However, chemotherapy remains the backbone of treatment.[5]

Oxaliplatin is part of the standard adjuvant treatment of colon cancer, and of the standard palliative treatment of distant metastases. A common toxic effect of oxaliplatin is a peripheral sensory neurotoxicity, which is often bothersome and sometimes debilitating for patients. In retrospective studies calcium and magnesium (Ca/Mg) infusions have been reported to prevent this toxicity.[6,7] However, concerns about a negative impact of Ca/Mg infusions on the efficacy of treatment in a prospective study have been raised,[8] which was later refuted.[9] We retrospectively assessed the effect of Ca/Mg infusions on toxicity and outcome in advanced colorectal cancer (ACC) patients treated in the phase III randomized CAIRO2 study.[10]

2. Patients and methods

2.1. Patients and treatment

The study population consisted of 755 previously untreated ACC patients from 79 Dutch hospitals who participated in the phase III CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG), which has been described in detail elsewhere.[10,11] In summary, patients were randomized between capecitabine, oxaliplatin and bevacizumab (CB) or the same regimen with the addition of cetuximab (CBC). Pre-existing neurotoxicity grade > 1 was an exclusion criterion to the study. The administration of oxaliplatin was limited to a maximum of six cycles in order to prevent severe neurotoxicity.[12] Oxaliplatin was given intravenously (i.v.) at 130 mg/m^2 during a 2 h infusion, every 3 weeks on day 1 of cycles 1–6, bevacizumab at 7.5 mg/kg i.v. on day 1 of each cycle, and capecitabine was taken orally twice daily for 14 d at 1000 mg/m^2 (total daily dose 2000 mg/m^2) during the first six cycles and at 1250 mg/m^2 (total daily dose 2500 mg/m^2) as of cycle seven, and cetuximab weekly at a first dose of 400 mg/m^2 in 2 h i.v. and subsequent doses at 250 mg/m^2 in 1 h i.v. All adverse events were evaluated before each treatment cycle (e.g. every 3 weeks) and graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. Tumour response rate (RR) was assessed by the local investigators every 9 weeks with the use of computed tomographic scans, according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. [13]

The prophylactic use of Ca/Mg infusions to prevent oxaliplatin-related sensory neurotoxicity was left to the discretion of the treating physician. The suggested dose was calcium glubionate 2.25 mmol + MgCl 4 mmol in 100 ml glucose 5%, i.v. in 15 min, before and after oxaliplatin infusion.

2.2. Study design

We retrospectively divided patients into two groups: the Ca/Mg$^+$ group, defined as patients having received Ca/Mg infusions during at least their first oxaliplatin cycle, and the Ca/Mg$^-$ group, defined as patients who did not receive Ca/Mg infusions during cycle 1. This definition was used to prevent a potential bias caused by the administration of Ca/Mg infusions for secondary prevention. In order to more accurately evaluate the relationship between oxaliplatin and neurotoxicity, we divided the incidence of sensory neurotoxicity into two subgroups: early toxicity, defined as neurotoxicity occurring during the first six treatment cycles (e.g. during oxaliplatin administration), and late neurotoxicity, defined as neurotoxicity which was present at the last cycle that patients received before going off study. Only patients who received seven or more treatment cycles were evaluable for late toxicity.

2.3. Statistical analysis

All eligible patients were analysed according to the intention-to-treat principle. All eligible patients who received at least one dose of study medication were evaluable for this analysis. Differences in toxicity between Ca/Mg$^+$ and Ca/Mg$^-$ groups within the total CAIRO 2 study population and within each treatment arm were compared using the Chi-square test. Progression-free survival (PFS) was defined as the interval from randomisation to first documented progression, death, or last follow-up, whichever came first, and patients who were alive without progression were censored from the date of their last follow-up. Overall survival (OS) was defined as the interval from randomisation to death or last follow-up. Survival curves were estimated with the Kaplan–Meier method and compared using a log-rank test. The response rate (RR) was defined as the rate of complete and partial responses and patients who completed at least 3 cycles were evaluable for response.

3. Results

Seven hundred and thirty two patients were evaluable for this retrospective analysis. Nineteen patients were excluded due to ineligibility and four patients were excluded as they did

not receive any study medication. The Ca/Mg$^+$ group consisted of 551 patients, 270 in the CB arm and 281 in the CBC arm. Of these patients 369 (67%) received Ca/Mg at all 6 oxaliplatin infusions. The Ca/Mg$^-$ group consisted of 181 patients (25%), 96 in the CB arm and 85 in the CBC arm. In this group 133 patients (73%) also did not receive any Ca/Mg infusions during subsequent oxaliplatin cycles. Baseline characteristics were comparable for patients in the Ca/Mg$^+$ group and the Ca/Mg$^-$ group (Table 1). A total of 139 patients discontinued all study medication for reasons of toxicity, 19% in the Ca/Mg$^+$ group and 19% in the Ca/Mg$^-$ group ($p = 0.94$). Median duration of follow-up was 34.8 months (95% confidence interval [CI] 33.6–37.3).

3.1. *Preventive effect of Ca/Mg infusions on neurotoxicity*

The incidence of all grade sensory neurotoxicity was 85% in the Ca/Mg$^+$ group and 92% in the Ca/Mg$^-$ group ($p = 0.02$, Table 2). Grade $\geqslant 2$ neurotoxicity occurred in 40% of the patients in Ca/Mg$^+$ group versus 45% of the patients in the Ca/Mg$^-$ group ($p = 0.22$). All grade early neurotoxicity (e.g. during the first 6 oxaliplatin-containing cycles) occurred significantly more often in the in the Ca/Mg- group than in the Ca/Mg$^+$ group (91% versus 81%, $p = 0.002$). We did not observe a significant difference in the incidence of early grade $\geqslant 2$ neurotoxicity (27% in the Ca/Mg$^+$ group versus 34% in the Ca/Mg$^-$ group, $p = 0.06$). The incidence of all grade late neurotoxicity was 30% in the Ca/Mg$^+$ group and 39% in the Ca/Mg$^-$ group ($p = 0.07$). Again, the incidence of grade $\geqslant 2$ late toxicity was comparable between both groups. No difference in the incidence of neurotoxicity was observed between patients treated in the CB compared to the CBC treatment arm.

When patients in the Ca/Mg$^+$ group who received Ca/Mg during all six oxaliplatin-containing cycles were compared to patients who received <6 Ca/Mg infusions no difference in the incidence of neurotoxicity was found. When patients in the Ca/Mg$^-$ group who received no Ca/Mg during all cycles were compared to patients within the Ca/Mg$^-$ group who received 1 or more Ca/Mg infusions at later cycles no difference in the incidence of neurotoxicity was found (data not shown).

3.2. *Effect of Ca/Mg infusions on the efficacy of treatment*

The median number of treatment cycles was 9 in both the Ca/Mg$^+$ and the Ca/Mg$^-$ group ($p = 0.88$). The percentage of patients receiving all 6 planned cycles of oxaliplatin was 70% and 71%, respectively ($p = 0.85$). The relative dose-intensity of oxaliplatin was comparable between both groups (mean relative dose-intensity oxaliplatin of 96.4% in the Ca/Mg$^+$ group versus 96.2% in the Ca/Mg$^-$ group, $p = 0.88$).

We observed no differences between the Ca/Mg$^+$ and Ca/Mg$^-$ group in median PFS (10.1 months versus 10.7 months, respectively, $p = 0.92$, HR 1.02 (0.83–1.24), Fig. 1), median OS [19.8 months versus 20.7 months, respectively, $p = 0.10$, HR 1.18 (0.97–1.44), Fig. 2] and overall best response rate (43% versus 50%, respectively, $p = 0.11$, Table 3). When the effect of Ca/Mg infusions was analysed per treatment arm (CB versus CBC), we also observed no significant differ-

Table 1 – Baseline characteristics of patients in Ca/Mg$^+$ and Ca/Mg$^-$ groups.

	Ca/Mg$^+$ group N = 551	Ca/Mg$^-$ group N = 181	p-value
Treatment group			0.35
CB	270 (49%)	96 (53%)	
CBC	281 (51%)	85 (47%)	
Age			0.05
Mean (range)	62.8 (27.0–83.0)	61.1 (41.0–79.0)	
Gender			0.38
Male	334 (61%)	103 (57%)	
Female	217 (39%)	78 (43%)	
Prior adjuvant treatment			0.67
Yes	80 (15%)	24 (13%)	
No	471 (85%)	157 (87%)	
Serum LDH			1.00
Normal	307 (56%)	101 (56%)	
Above normal	243 (44%)	80 (44%)	
Missing	1 (0.2%)		
Numbers of metastatic sites			0.10
1 site	179 (32%)	71 (39%)	
>1 site	372 (68%)	110 (61%)	
WHO Performance Status			0.68
0	343 (62%)	116 (64%)	
1	207 (38%)	65 (36%)	
Missing	1 (0.2%)		

CB, capecitabine, oxaliplatin and bevacizumab; CBC, capecitabine, oxaliplatin, bevacizumab and cetuximab; LDH, lactate dehydrogenase; WHO, World Health Organization; and N, number of patients.

Table 2 – Effect of Ca/Mg infusions on the incidence of neurotoxicity.

All patients	Ca/Mg^+ group $N = 551$	Ca/Mg^- group $N = 181$	*p*-value
All grade	466 (85%)	166 (92%)	0.02
Grade 1	248 (45%)	85 (47%)	
Grade 2	172 (31%)	59 (33%)	
Grade 3	46 (8%)	22 (12%)	
Grade ⩾ 2	218 (40%)	81 (45%)	0.22
Early toxicity[a]			
All grade	444 (81%)	164 (91%)	0.002
Grade 1	296 (54%)	102 (56%)	
Grade 2	127 (23%)	48 (27%)	
Grade 3	21 (4%)	14 (8%)	
Grade ⩾ 2	148 (27%)	62 (34%)	0.06
Late toxicity[b]	$N = 356$	$N = 123$	
All grade	107 (30%)	48 (39%)	0.07
Grade 1	75 (21%)	34 (28%)	
Grade 2	28 (8%)	9 (7%)	
Grade 3	4 (1%)	5 (4%)	
Grade ⩾ 2	32 (9%)	14 (11%)	0.44
Treatment discontinuation for toxicity			
All patients	105 (19%)	34 (19%)	0.94

N, number of patients.
[a] Toxicity during cycles 1–6.
[b] Toxicity present at the last cycle that patients received before going of study, in patients who received >6 cycles.

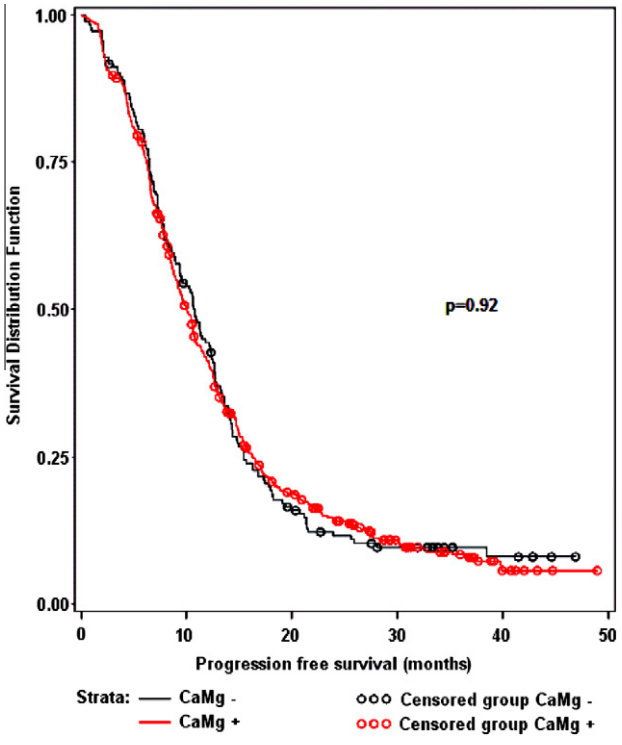

Fig. 1 – Progression-free survival (PFS) in patients with and without Ca/Mg infusions.

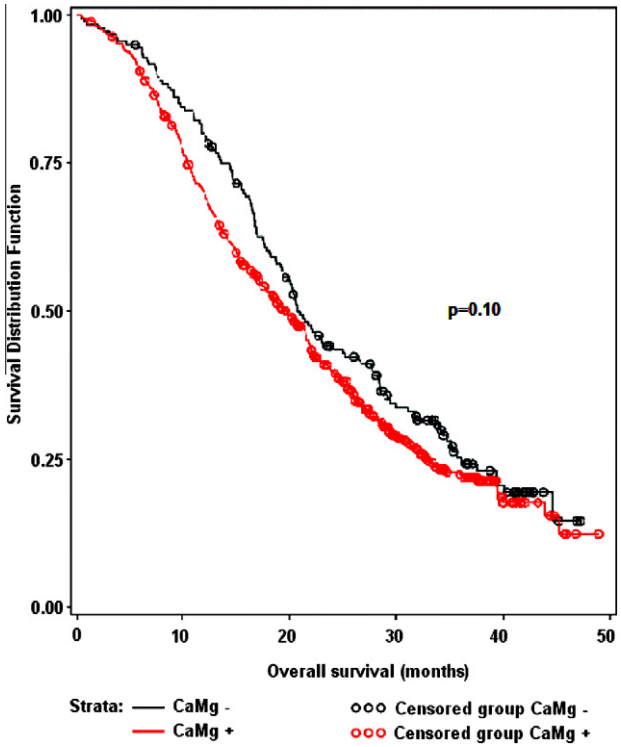

Fig. 2 – Overall survival in patients with and without Ca/Mg infusions.

ences in outcome. In the CB group the median PFS in the Ca/Mg^+ group versus the Ca/Mg^- group was 10.8 and 10.6 months, respectively [$p = 0.62$, HR 0.86 (0.65–1.13)], the median OS was 19.8 and 21.7 months, respectively [$p = 0.52$, HR 1.10 (0.83–1.44)], and the RR was 43% and 46%, respectively ($p = 0.63$). In the CBC group the median PFS in the Ca/Mg^+ group versus

Table 3 – Effect of Ca/Mg Infusions on treatment outcome.

All patients	Ca/Mg^+ group N = 551	Ca/Mg^- group N = 181	p-value
Median PFS (months)	10.1	10.7	0.92
Median OS (months)	19.8	20.7	0.10
Response rate (CR + PR)	43.1%	50.0%	0.11
% of patients that received six cycles oxaliplatin	70.0%	70.7%	0.85
CB group	N = 270	N = 96	
Median PFS (months)	10.6	10.8	0.62
Median OS (months)	19.8	21.7	0.52
Response rate	42.5%	45.5%	0.63
CBC group	N = 281	N = 85	
Median PFS (months)	9.2	11.0	0.60
Median OS (months)	18.9	20.6	0.11
Response rate	43.6%	54.9%	0.07

the Ca/Mg^- group was 9.2 months and 11.0 months, respectively [$p = 0.60$, HR 1.18 (0.89–1.57)], the median OS was 18.9 months and 20.6 months, respectively [$p = 0.11$, HR 1.26 (0.95–1.68)] and the RR was 44% and 55%, respectively ($p = 0.07$).

4. Discussion

We retrospectively investigated in a large phase III study in ACC patients the effect of Ca/Mg infusions on the incidence of oxaliplatin-related neurotoxicity and on the efficacy of treatment with capecitabine, oxaliplatin and bevacizumab with or without cetuximab. We observed a significant reduction of all grade neurotoxicity in patients who received Ca/Mg infusions, which difference was highly significant for neurotoxicity occurring early during treatment, i.e. during the first 6 oxaliplatin-containing cycles. Ca/Mg infusions did not prevent the occurrence of severe (grade $\geqslant 2$) neurotoxicity. Although a trend towards an inferior OS and RR was observed in patients who received Ca/Mg infusions, there was no statistically significant effect of Ca/Mg infusions on the overall RR, median PFS and median OS in the overall study population.

In our study the administration of oxaliplatin was limited to a maximum of six cycles in order to prevent severe neurotoxicity. This is based on the findings of the OPTIMOX study[12] that showed a more favourable toxicity profile for a limited versus prolonged oxaliplatin administration without compromising the survival outcome. Our results therefore do not preclude a more significant benefit from Ca/Mg infusions in patients receiving more than 6 cycles of oxaliplatin. The prophylactic use of Ca/Mg infusions has been the subject of debate, since the initial data on its preventive effect of oxaliplatin-induced neurotoxicity were derived from a retrospective study, and concerns about a negative impact on the clinical efficacy of treatment have been raised in a prospective study. Gamelin and colleagues[14] retrospectively analysed the effect of Ca/Mg infusions in 161 ACC patients treated with oxaliplatin-based chemotherapy, and observed a significant decreased incidence of acute and chronic neurotoxicity in the 96 patients who had received prophylactic Ca/Mg infusions. No effect on tumour response rate was noted.

The preventive effect of Ca/Mg infusions was subsequently tested in a prospective trial in ACC patients treated with oxaliplatin and bevacizumab (CONcePT trial). This trial was early terminated due to a lower response rate in patients who received Ca/Mg infusions.[15] However, subsequent independent review of CT scans from 140 randomized patients in this trial showed no significant difference in response or time to first response for patients receiving Ca/Mg infusions when compared to placebo.[9] The N04C7 trial, a double blind randomized study of Ca/Mg infusions versus placebo in ACC patients treated with FOLFOX was temporary on hold in view of the preliminary reports from the CONcePT trial. Analysis of the 102 patients enrolled in the N04C7 study showed a decrease of grade > 2 neurotoxicity in patients receiving Ca/Mg infusions (22% versus 38.5%, $p = 0.07$).[16] Preliminary data of the Neuroxa-trial, a double blind randomized study of Ca/Mg infusions versus placebo in ACC patients treated with FOLFOX showed no difference in RR, PFS and OS between the two groups, but only 54 patients were analysed.[17]

An obvious limitation of our subgroup analysis is its retrospective nature, which potentially may have introduced a selection bias. However, this seems unlikely, given the fact that the decision to administer Ca/Mg infusions was largely driven by treatment site and not by individual patient characteristics or preferences, as the policy to administer or not to administer Ca/Mg infusions was consistent in 87% of participating centres. Also the baseline patient characteristics were quite similar between the Ca/Mg^+ and Ca/Mg^- groups.

We have assessed neurotoxicity by NCI-CTC. The quality of life analysis in the clinical trial was performed using the EORTC QLC questionnaire and did not incorporate any specific questions on neurotoxicity-related symptoms. Due to the retrospective nature of this analysis we are not able to assess neurotoxicity by other scales than the NCI-CTC. Therefore we have no data on patient reported outcome of neurotoxicity. In conclusion, we demonstrate in the largest retrospective analysis in ACC patients to date that Ca/Mg infusions significantly reduce the likelihood of all grade neurotoxicity, although the effect appears to be largely restricted to grade 1 neurotoxicity. Ca/Mg infusions had no significant effect on the efficacy of treatment. Our results support the safety and

modest efficacy of prophylactic Ca/Mg infusions in patients treated with oxaliplatin-based systemic treatment.

CAIRO team members

Medical Oncology Task Force of the Dutch Colorectal Cancer Group: E. Balk, J.W.R. Nortier, A. Cats, C.J.A. Punt, C.J. van Groeningen, D.J. Richel, R.L.H. Jansen, H.P. Sleeboom, J.J.M. van der Hoeven, J. Verweij, A.S.Th. Planting, R.S. de Jong, E.E. Voest, N.H. Mulder.

The following investigators participated in undertaking the CAIRO2 study: C. Smorenburg, Alkmaar; R. Hoekstra, Almelo; C. Rodenburg, Amersfoort; J. van der Hoeven, Amstelveen; A. Cats, M. Geenen, C. van Groeningen, D. Richel, B. de Valk, N. Weijl, Amsterdam; J. Douma, Arnhem; P. Nieboer, Assen; F. Valster, Bergen op Zoom; R. Rietbroek, Beverwijk; A. Ten Tije, Blaricum; O. Loosveld, Breda; D. Kehrer, Capelle a/d IJssel; M. Bos, Delft; Z. Erjavec, Delfzijl; H. Sinnige, C. Knibbeler, Den Bosch; W. Van Deijk, F. Jeurissen, H. Sleeboom Den Haag; A. Imholz, Deventer; E. Muller, Doetinchem; J. vanden Bosch, Dordrecht; S. Hovenga, Drachten; E. Balk, Ede; G. Creemers, M. Dercksen, Eindhoven; M. Legdeur, Enschede; A. Smals, Geldrop; H. van Halteren, Goes; M. van Hennik, Gorinchem; A. van der Torren, Gouda; G. Hospers, R. de Jong, Groningen; G. de Klerk, Haarlem; P. Zoon, Harderwijk; J. Wals, Heerlen; V. Derleyn, Helmond; H. Dankbaar, Hengelo; S. Luyckx, Hilversum; C. de Swart, Hoofddorp; J. Haasjes, Hoogeveen; W. Meijer, Hoorn; M. Polee, Leeuwarden; M. Tesselaar, Leiden; H. Oosterkamp, Leidschendam; J. Bollen, Lelystad; R. Jansen, Maastricht; P. van der Velden, Middelharnis; P. Slee, Nieuwegein; C. Punt, C. Mandigers, Nijmegen; A. Vos, Oss; M. den Boer, Roermond; D. de Gooyer, Roosendaal; A. Planting, A. vander Gaast, J. Pegels, T. Kok, F. de Jongh, Rotterdam; J. Braun, Schiedam; F. Erdkamp, Sittard; G. Veldhuis, Sneek; A. van Reisen, Terneuzen; C. Kruijtzer, Tiel; H. Roerdink, J. van Riel, Tilburg; D. ten Bokkel Huinink, E. Voest, Utrecht; M. van Diemen, Veghel; G. Vreugdenhil, Veldhoven; M. Werter, Venlo; L. Kerkhofs, Vlissingen; P. Schiphorst, Winterswijk; A. van Bochove, Zaandam; A. Ogilvie, Zoetermeer; A. Honkoop, Zwolle.

Independent Data Monitoring Committee: P. De Mulder (deceased), D. Sleijfer, G. Stoter.

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Conflict of interest statement

None declared.

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