Health-related quality of life after isolated limb perfusion compared to extended resection, or amputation for locally advanced extremity sarcoma: Is a limb salvage strategy worth the effort?

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Introduction: The aim of this study was to compare long-term patient reported outcomes (PROs) in patients with locally advanced extremity soft tissue sarcoma (eSTS) after isolated limb perfusion followed by resection (IR), compared to extended resection (ER), primary amputation (A) or secondary amputation after IR (IR-A).

Methods: Patients were selected from the respondents of a multi-institutional cross-sectional cohort survivorship study (SURVSARC) conducted among sarcoma survivors registered in the Netherlands Cancer Registry (NCR), 2–10 years after diagnosis. Used PROs were the EORTC QLQ-C30, the Cancer worry scale (CWS), the Hospital Anxiety and Depression Scale (HADS), and the Toronto Extremity Salvage Score (TESS).

Results: We identified 97 eSTS survivors: IR = 20, ER = 49, A = 20, IR-A = 8. While there were no differences in PROs between IR and ER, results showed better functioning and functionality in both groups versus the amputation groups. The amputation groups scored significantly lower on physical functioning (A = 62.7, IR-A = 65.7 versus IR = 78.0, ER = 82.7, p = 0.001) and role functioning (A = 67.5, IR-A = 52.8 versus IR = 79.2, ER = 80.6, p = 0.039), both EORTC QLQ-C30 scales. Also for the TESS, the scores were significantly lower for the amputation groups compared to the limb sparing groups (upper extremity p < 0.001 with A = 68.9, IR-A = 71.6 versus IR = 93.3, ER = 91.1; lower extremity p < 0.001 with A = 72.2, IR-A = 84.5 and ER = 85.5). There were no significant differences between the groups on cancer worry, anxiety and depression.

Conclusion: HRQoL in eSTS survivors treated with IR or ER is equal; for maintenance of physical functioning and functionality IR and ER outperform an amputation.

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1. Introduction

Limb salvage surgery (LSS) is the cornerstone of treatment for extremity soft tissue sarcoma (eSTS) [1]. Wide local excision is often combined with (neo)adjuvant radiotherapy, or to a lesser extent
with (neo)adjuvant chemotherapy in high risk sarcomas. For locally advanced primary, as well as recurrent eSTS, an extended resection is often indicated, and some tumors may need amputation for adequate local disease management [2,3]. These extended resections may comprise debulking of a whole extremity compartment, occasionally including resection of vasculature and nerves.

While radiotherapy does not lead to tumor size reduction in most cases, isolated limb perfusion (ILP) frequently downsizes locally advanced tumors, potentially allowing for LSS [4–7]. An ILP involves isolation of the limb vascular system from the systemic circulation, allowing administration of dose intensified cytotoxic therapies (mostly TNFα and Melphalan) with acceptable toxicity [8]. Using this strategy, limb salvage rates (LSR) of 62–96% have been reported, with overall response rates (ORR) ranging from 61 to 90% and complete response rates (CRR) of 17–59% [4–7,9–16].

Although the limb salvage rate is relatively high in eSTS, the response to ILP is not always sufficient to prevent amputation, resulting in a secondary amputation. Also, in a small percentage of patients, toxicity of ILP may lead to a treatment induced amputation (Wieberdink grade V) [17]. Since amputations are major procedures with potentially profound implications such as increased degree of disability and post amputation pain (PAP), they are usually only performed as a last resort when no other options are available, based on a balance between expectations of functional and oncological outcome. No survival differences have been demonstrated between the different local surgical treatments, which can be explained by the fact that survival is mainly determined by distant metastases [3,18,19].

While ILP is usually considered a safe and well tolerated procedure, given the (very) low risk of major complications, health-related quality of life (HRQoL) should be taken into account when considering ILP. Although there is ample literature discussing ILP and limb salvage rate, data discussing long-term HRQoL after ILP compared to extended resections or amputation in eSTS is scarce. Therefore, the aim of this study is to analyze long term HRQoL (including functioning and symptoms) and other PROs (such as limb functionality, cancer worry, anxiety and depression) after ILP followed by resection, compared to extended resection or amputation after ILP for locally advanced eSTS.

2. Methods

Patients were selected from the database of a multi-institutional cross-sectional cohort study (SURVSARC), conducted among all sarcoma survivors who were registered in the Netherlands Cancer Registry (NCR) and have been diagnosed and treated between 1-1-2008 and 31-12-2016 within one of the six participating Dutch sarcoma centers (Netherlands Cancer Institute [Amsterdam], Erasmus Medical Centre [Rotterdam], Leiden University Medical Centre, Radboud University Medical Centre [Nijmegen], University Medical Centre Groningen, Maastricht University Medical Centre). Ethical approval was granted by the medical ethical committee of the Radboud University Medical Centre (2017–3944), and the study was registered in the Dutch Trial Registry (NTR-7235).

The study assessed subjective PRO’s like HRQoL and illness related symptoms from sarcoma survivors on one single time point 2–10 years after diagnosis, by means of a self-administered questionnaire composed of several validated questionnaires [20]. From these questionnaires, we selected questions regarding surgery related outcomes and the following HRQoL questionnaires: the EORTC QLQ-C30, the Cancer worry scale (CWS), the Hospital Anxiety and Depression Scale (HADS) and the Toronto Extremity Salvage Score (TESS). The questionnaire also covered patient reported treatment details, because the NCR contains treatment data of the primary tumor (registered 6–9 months after diagnosis) and since 2016 treatment data on recurrent disease within 3 years after primary diagnosis. From the NCR socio-demographic and clinical characteristics (such as gender, age, tumor subtype, tumor grade, stage at diagnosis, tumor-location, primary treatment, and time since diagnosis) were extracted.

The general response rate of the study was 58%; 1099 patients were included [20]. Of these respondents, 576 were extremity sarcoma survivors. After excluding the bone sarcoma patients (N = 136), we selected eSTS survivors based on some specific patient reported surgical treatments (IR, ER, A and IR-A), see Fig. 1. To identify these patients with a presumably extended resection (ER group) from the NCR, which lacks specific tumor and surgical specifications, we defined an extended resection as all patients that received surgery for stage III STS, meaning tumors of at least 5 cm and at least grade 2 according to FFCCSG classification [21]. Patients without resection (n = 8), tumor stage unknown (n = 42) and resection for < stage III disease (low grade or ≤ 5 cm tumors, n = 293) were categorized as ‘other’, see Fig. 1. Details regarding amputation levels other than upper or lower extremity are unknown.

2.1. EORTC health related quality-of-Life Questionnaire (QLQ-C30)

The EORTC QLQ-C30 is one of the most widely used cancer HRQoL questionnaires. It consists of 30 items assessing HRQoL across five functioning scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), three multi-item symptom scales (fatigue, pain, nausea and vomiting), six single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems) and global quality-of-life (QoL) [22]. Scores range from 0 to 100 after transformation by linear transformation following the QLQ-C30 scoring manual [23]. A higher score on the functioning scales and on global QoL represent a better level of functioning and global QoL, and a higher score on the symptom scales means a higher level of symptoms.

2.2. Cancer worry scale (CWS)

Cancer worry scale (CWS) assesses the concerns about the recurrence of cancer and the impact of these concerns on daily functioning among individuals at risk for (hereditary) cancer [24].

The Dutch version of the CWS has two extra items compared to the original questionnaire, which address focus on family members and future surgery [25]. Higher (>14) scores indicate more frequent worries about cancer.

2.3. Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) has two subscales to indicate the levels of anxiety and depression during the last week [26]. Higher (>8) scores indicate more anxiety, depressive symptoms, and psychological distress.

2.4. Toronto Extremity Salvage Score (TESS)

While the EORTC QLQ-C30 is a generic cancer HRQoL questionnaire which also briefly addresses physical functionality, the Toronto Extremity Salvage Score (TESS) is a specific validated questionnaire that assesses functional outcomes in patients with musculoskeletal tumors of the extremity [27]. Separate questionnaires exist for both the upper (29 questions) and lower limb (30 questions), with the questions being specifically tailored to the
function of the extremity. The raw score is converted to a total score ranging from 0 to 100 (percentage), with higher scores indicating less functional limitations.

2.5. Statistical analysis

All analyses were performed in IBM SPSS 25.0 for Windows (version 25) with a significance level of $\alpha = 0.05$. Patient characteristics, disease related data and operation effects were compared between the 4 groups with the Kruskal Wallis tests in case of numerical variables (without normal distribution) and Chi-Square tests in case of categorical variables. One-way ANOVA tests (to allow for post-hoc comparisons) were used to compare all the HRQoL scores (EORTC QLQ-C30, CWS, HADS and TESS) and subscales were compared using the Chi-Square test. For post-hoc analyses we used the Bonferroni test of which we have not corrected the significance level, given the small group sizes and the exploratory nature of this secondary analysis. For the EORTC QLQ-C30, clinical relevance of differences between groups are defined by Cocks et al. [28]. For PF, the mean scores in the IR and ER group (LSS) were respectively 78.0 (SD 18.2) and 82.7 (SD 16.5), compared to 62.7 (SD 23.4) in the A group and 65.7 (SD 20.9) in the IR-A group ($p = 0.001$). Post Hoc test showed a specific significant difference between the ER and the A group ($p = 0.001$), but the difference between the LSS groups and the IR-A group was not statistically significant. For RF, the mean scores for the groups IR and ER were respectively 79.2 (SD 24.1) and 80.5 (SD 23.7), compared to 67.5 (SD 31.3) for the A group and 52.8 (SD 30.6) for the IR-A group ($p = 0.039$).

The only significant difference on the symptoms scales and/or items was for ‘nausea and vomiting’ with mean scores of 5.8 (SD 9.8) for IR, 1.0 (SD 4.0) for ER, 4.2 (SD 9.2) for A and 0 (SD 0) for IR-A ($p = 0.033$). In addition, ‘fatigue’ showed a non-significant difference of 14.6 (between 29.4 for the IR group and 14.8 for the IR-A group), which accounts for a difference with ‘medium’ clinical relevance [28]. No differences were seen in the groups between radiotherapy and non-radiotherapy patients.

3. Results

We selected a total of 97 survivors from the database who met our selection criteria: 20 survivors for the ILP followed by resection (IR) group (78 months (range 43–134) since diagnosis), 49 survivors for the extended resection (ER) group (52 months (range 23–133) since diagnosis), 20 survivors for the amputation (A) group (57 months (range 25–108) since diagnosis) and 8 survivors for the secondary amputation after IR (IR-A) group (96 months (range 25–126) since diagnosis), see Fig. 1. Patient and tumor related characteristics of the survivors can be found in Table 1. Most characteristics showed no differences between the groups, except for the application of radiotherapy, which was significantly less administered in the A group ($p < 0.001$), wherein the ER group almost all had radiotherapy (90%). Time from diagnosis to study was significantly longer in the ILP groups ($p = 0.004$) with a median overall follow-up time for the whole group of 60 months (range 23–134).

3.1. HRQoL

Most functioning scales showed no significant differences between the groups, except for the physical functioning (PF) scale and the role functioning (RF) scale, where the scores for the LSS groups (IR and ER) were higher when compared to the amputation groups (A and IR-A), see Table 2 and Fig. 2. Clinical relevance of differences in EORTC QLQ-C30 scores are defined by Cocks et al. [28]. For PF, the mean scores in the IR and ER group (LSS) were respectively 78.0 (SD 18.2) and 82.7 (SD 16.5), compared to 62.7 (SD 23.4) in the A group and 65.7 (SD 20.9) in the IR-A group ($p = 0.001$). Post Hoc test showed a specific significant difference between the ER and the A group ($p = 0.001$), but the difference between the LSS groups and the IR-A group was not statistically significant. For RF, the mean scores for the groups IR and ER were respectively 79.2 (SD 24.1) and 80.5 (SD 23.7), compared to 67.5 (SD 31.3) for the A group and 52.8 (SD 30.6) for the IR-A group ($p = 0.039$).

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group, with \( p = 0.002 \) for the IR group and \( p = 0.001 \) for the ER group. In the IR-A group, the lower extremity results were worse than the upper extremity scores (difference of 20.69 points), which is also seen to a lesser extent in the LSS groups. No differences were observed in the groups between patients that received radiotherapy and patients that did not receive radiotherapy.

### 3.4. Late effects of surgery

In both the ER and the IR group, 55% evaluated their scar as ugly, in contrast to 30% in the A group and 12% in the IR-A treatment group, which was statistically significant different (\( p = 0.001 \)). Multiple survivors reported inconvenience caused by their scar, as shown in Table 4. Wound issues were not statistically different between the groups. From the survivors who were treated by means of amputation, 11 survivors (55%) had post amputation pain (PAP) in the A group and 5 survivors (62.5%) in the IR-A treatment group.

### 4. Discussion

In this study, we showed that physical functioning and functionality after limb salvage by ILP was significantly better than after amputation for locally advanced eSTS, while physical functioning and functionality after ILP and extended resections did not differ. No differences were found on other HRQoL domains. These results suggest that an ILP for patients who otherwise would undergo an amputation or highly morbid surgery is justified and lead to better HRQoL, while amputations in patients with eSTS lead to decreased HRQoL without survival benefit. To our knowledge, this is the first HRQoL-focused study comparing ILP to both amputations and larger resections.

Our results showed nearly the same statistically significant differences as Thijssens et al., who compared ILP (\( n = 30 \)) and ILP + amputation (\( n = 9 \)) with a reference group (\( n = 1063 \), a random population sample without sarcoma) [29]. Most patients in their study received adjuvant radiotherapy as well. The study showed lower physical functioning and role limitations for the ILP patients, which is in line with our results as well. However, Podleska et al. [30] found no difference in HRQoL (EORTC QLQ-C30) and physical function (SMFA) between a group of STS patients undergoing ILP (\( n = 27 \)) and compared to the results of amputated osteosarcoma patients from Zahlten-Hinguranage et al. [31] (\( n = 22 \)) and to EORTC reference values for ‘general population’ and ‘all cancer patients’. However, this study compares different
<table>
<thead>
<tr>
<th>Scale/item</th>
<th>Limb salvage surgery</th>
<th>Amputation</th>
<th>Post hoc analysis (Bonferroni) Clinical relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional scales</strong></td>
<td></td>
<td></td>
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<tr>
<td>Physical functioning (PF)</td>
<td>78.0</td>
<td>18.2</td>
<td>Medium</td>
</tr>
<tr>
<td>Role functioning (RF)</td>
<td>79.2</td>
<td>20.7</td>
<td>Medium</td>
</tr>
<tr>
<td>Emotional functioning (EF)</td>
<td>82.5</td>
<td>19.8</td>
<td>Medium</td>
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<tr>
<td>Cognitive functioning (CF)</td>
<td>87.5</td>
<td>17.0</td>
<td>Medium</td>
</tr>
<tr>
<td>Social functioning (SF)</td>
<td>86.1</td>
<td>17.2</td>
<td>Medium</td>
</tr>
<tr>
<td><strong>Symptom scales and/or items</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue (FA)</td>
<td>29.4</td>
<td>23.7</td>
<td>Medium</td>
</tr>
<tr>
<td>Nausea and vomiting (NV)</td>
<td>5.8</td>
<td>5.8</td>
<td>Medium</td>
</tr>
<tr>
<td>Appetite loss (AP)</td>
<td>5.0</td>
<td>5.0</td>
<td>Medium</td>
</tr>
<tr>
<td>Constipation (CO)</td>
<td>5.0</td>
<td>5.0</td>
<td>Medium</td>
</tr>
<tr>
<td>Pain (FI)</td>
<td>11.7</td>
<td>11.7</td>
<td>Medium</td>
</tr>
</tbody>
</table>

*Between the extended resection group and the amputation group.*

**Large clinical difference: unequivocal clinical relevance. Medium clinical relevance: likely to be clinically relevant but to a lesser extent. Small clinical relevance: subtle but nevertheless clinically relevant. Trivial clinical relevance: unlikely to have any clinical relevance.**

**Statistically significant lower scores on the EORTC QLQ-C30 PF and TESS for this group due to late radiotherapy side effects.** However, this is not reflected in the results in the IR-A group compared to the upper extremity, especially in the IR-A group, but the lower extremities resulted in non-statistically lower functionality. In our study, physical limitations were overt in both amputation groups as measured by the statistically significant lower scores on the EORTC QLQ-C30 PF scale. The EORTC QLQ-C30 RF scale was also significantly lower in the amputation groups, which is not surprising as this is very much related to PF, because it assesses the ability of a patient to perform daily activities, work and/or leisure-time activities, which can be affected when missing a (part of a) limb. Statistically significant lower TESS scores for both amputation groups confirms the EORTC QLQ-C30 RF scores, again indicating the impact of the loss of a (part of a) limb in addition, involvement of the lower extremities resulted in non-statistical lower functionality compared to the upper extremity, especially in the IR-A group, but the numbers of the subgroups were low. The results in the IR-A group were on some scales worse than the A group, however, these differences were not statistically significant. The fact that a high percentage of survivors in the ER group had additional radiotherapy could potentially negatively affect scores on the EORTC QLQ C30 PF scale and TESS for this group due to late radiotherapy side effects. However, this is not reflected in our results since there were no statistically significant differences between patients receiving radiotherapy or not receiving radiotherapy in the different groups.

It is notable that the EORTC QLQ-C30 PF and RF are the only two scales with statistical lower scores without affecting the other scales, such as social functioning, and it raises the question whether the EORTC QLQ-C30 questionnaire, which has never been validated for amputees, is applicable to survivors with amputation. However, physical discomfort does not always translate into a decrease in other domains of HRQoL.

Although there is no difference in distance metastases between the different surgical approaches [3,18,19], the risk of local recurrence is lower in case of an amputation. However, no difference in fear of cancer recurrence in favor of the amputation group was observed in our study. Also, no differences were found in anxiety or depression between the different eSTS survivor groups. Shared decision making with the patient on either IR, ER or A may be an explanation for this observation.

Despite the fact that we expected a cosmetic benefit from limb-sparing surgery, survivors with an amputation were more satisfied with their scar. The most plausible explanation is that the impact of an amputation is already much more profound compared to a limb sparing resection, which makes the appearance of the scar itself irrelevant. Our questionnaire unfortunately did not address body image, which was negatively affected in previous research by groups from different studies with different diseases, making their comparison not entirely valid.
post-treatment effects and caused a decrease in HRQoL [39].

Our study has several novel findings: first, we present the results of a population-based survivorship study with participation of 6 sarcoma centers and validated questionnaires. Compared to other studies which were mostly monocenter, our study also has the largest group of survivors with one of the longest follow-up periods and is the first to compare all different local treatment options for locally advanced eSTS.

However, our study has several limitations. First of all, the number of included survivors who underwent certain special treatments is relatively low (especially the IR-A is small, n = 8), which reflects the high percentage of successful ILP's and is consistent with what we see in daily practice. Secondly, all data regarding tumor characteristics or treatment are either based on PRO's or the national registry and therefore several details are not available. Unfortunately, data is also missing regarding disease status at the time of the study and treatments undertaken for any recurrent or metastatic disease, which could affect the HRQoL. A third limitation is that there might be an underrepresentation of stage III tumors in this study, which could be explained by a potential survivorship bias given the relatively poor prognosis of stage III patients. Fourth, there is a (non-) respondent bias, since only 58% of all NCR registered survivors with eSTS in the participating centers did complete their questionnaire. The last limitation is that the symptoms and limitations survivors experience in their daily life may not always be due to the diagnosis (2–10 years ago) or treatment of their eSTS (recall bias) and the fact that patient reported data is not always reliable in their specificity when it comes to objective clinical data. In addition, it is important to acknowledge that ILP is relatively widely available in the Netherlands with 3 centers that provide this treatment, on a total population of around 17 million.

An improvement in future HRQoL research could be longitudinal studies with multiple measurements, which bypasses a possible recall bias and could give even more information on the course of HRQoL over time. As reported by van Eck et al., a more specified

### Table 3

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Limb salvage surgery</th>
<th>Amputation (A) (n = 20)</th>
<th>ILP + amputation (IR-A) (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer worry scale (CWS)</td>
<td>ILP + resection (IR) (n = 20) 14.5 ± 6.4 20 60%</td>
<td>Amputation (A) (n = 20) 14.1 ± 4.9 19 53%</td>
<td>Amputation (IR-A) (n = 8) 13.0 ± 3.6 7 57%</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
<td>Extended resection (ER) (n = 49) 13.5 ± 4.0 49 59%</td>
<td>Amputation (A) (n = 20) 10.5 ± 3.6 53 57%</td>
<td>Amputation (IR-A) (n = 8) 9.4 ± 4.7 47 57%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Low (&lt;7) 4.5 ± 3.6 12 60%</td>
<td>Low (&lt;7) 4.1 ± 3.6 13 68%</td>
<td>Low (&lt;7) 5.2 ± 3.4 11 68%</td>
</tr>
<tr>
<td>High (&gt;8)</td>
<td>3.7 ± 3.6 20 60%</td>
<td>3.6 ± 3.4 16 53%</td>
<td>3.6 ± 3.3 14 53%</td>
</tr>
<tr>
<td>Depression</td>
<td>Low (&lt;7) 4.5 ± 3.6 12 60%</td>
<td>Low (&lt;7) 4.1 ± 3.6 13 68%</td>
<td>Low (&lt;7) 5.2 ± 3.4 11 68%</td>
</tr>
<tr>
<td>High (&gt;8)</td>
<td>3.7 ± 3.6 20 60%</td>
<td>3.6 ± 3.4 16 53%</td>
<td>3.6 ± 3.3 14 53%</td>
</tr>
<tr>
<td>Toronto Extremity Salvage Score (TESS)</td>
<td>Upper extremity 93.3 ± 7.3 3 15 60%</td>
<td>Upper extremity 91.1 ± 11.2 8 16 60%</td>
<td>Upper extremity 86.9 ± 17.1 6 30 60%</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>84.5 ± 13.6 16 80 60%</td>
<td>85.8 ± 13.1 16 80 60%</td>
<td>85.1 ± 17.4 16 80 60%</td>
</tr>
</tbody>
</table>

* Post Hoc test showed for TESS upper extremity a significant difference of p = 0.022 between amputation and the extended resection group. For the TESS lower extremity showed a significant difference of p = 0.002 between the ILP group and the ILP + amputation group and a p = 0.001 between the ILP + amputation group and the extended resection group.
HRQoL measurement is needed to capture more disease and treatment specific HRQoL, for example the EORTC QLQ C-30 supplemented with items from the EORTC Item Library, which is currently being investigated [40].

Despite all the limitations, this study illustrates that ILP can prevent a significant decrease in HRQoL, which would favor a more liberal use of ILP for patients otherwise needing an amputation. This does depend, however, on the availability of ILP per country.

5. Conclusion

In conclusion, ILP followed by resection has comparable long-term HRQoL results compared to extended resection and has superior functional patient reported outcome compared to patients undergoing an amputation. These results confirm and justify that ILP should be considered as induction therapy in order to prevent amputation, since this can prevent a decrease in HRQoL for patients undergoing a primary amputation, emphasizing the need to better select patients and histological subtypes potentially benefiting from an ILP and identifying risk factors for severe complications.

CRediT authorship contribution statement

Sophie J.M. Reijers: Conceptualization, Formal analysis, Validation, Investigation, Data curation, Writing – original draft, Visualization, Olga Husson: Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing, Visualization, Supervision, Project administration. Vicky L.M.N. Soomers: Conceptualization, Resources, Data curation, Writing – review & editing. Lukas B. Been: Conceptualization, Resources, Writing – review & editing. Johannes J. Bonenkamp: Conceptualization, Resources, Writing – review & editing. Michiel A.J. van de Sande: Conceptualization, Resources, Writing – review & editing. Cornelis Verhoef: Conceptualization, Resources, Writing – review & editing. Winette T.A. van der Graaf: Conceptualization, Methodology, Resources, Writing – review & editing, Visualization, Supervision. Winan J. van Houdt: Conceptualization, Methodology, Resources, Writing – original draft, Visualization, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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