Association Between Participant Retention and the Proportion of Included Elderly People in Rheumatology Trials: Results From a Series of Exploratory Meta-Regression Analyses

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Objective. The elderly, a population defined by an age of ≥65 years, are underrepresented in rheumatology trials, possibly due to investigators' concerns of increased premature discontinuations in higher age groups. The present study was undertaken to evaluate whether the proportion of included elderly individuals (PE) is independently associated with participant retention in rheumatology trials.

Methods. Medline was searched for randomized controlled trials (RCTs) in rheumatoid arthritis (RA) and osteoarthritis (OA) of any intervention (years 2016 and 2017). PE was either extracted from the research manuscript or estimated from an assumed (truncated) normal distribution. We used mixed-effects meta-regression models including several covariates to assess whether there is an independent association between PE and participant retention. Using sensitivity analyses, we evaluated whether associations were connected to attrition due to lack of efficacy (LoE) or adverse events (AE).

Results. In total, 243 RCTs comprising >48,000 participants were included. Pooled participant retention was 88%. PE was not associated with retention in the unadjusted ($P = 0.97$) or adjusted (all: $P \geq 0.14$) models. Of all covariates, only study duration and type of intervention were associated with retention (both: $P < 0.001$). Post hoc analyses allowing for interaction revealed a small but statistically significant positive association between PE and retention in pharmacologic interventions and a negative association in physical/physiotherapeutic interventions (overall P for interaction = 0.05). No associations were found for PE and attrition due to LoE or AE.

Conclusion. Participant retention in RA and OA trials is high and not associated with PE. These findings should motivate investigators to include more elderly participants in rheumatology trials.

INTRODUCTION

The elderly, a population commonly defined by an age of ≥65 years, are significantly underrepresented in current rheumatoid arthritis (RA) and osteoarthritis (OA) trials (1). This is a problem since older people differ from younger adults in multiple aspects, such as (but not limited to) comorbidities, pharmacodynamics, or polypharmacy (1–5). All of these may affect the risk–benefit ratio. As one example, elderly patients with RA have been shown to have a diminished response rate to biologic agents and generally a less beneficial risk–benefit ratio (6–8).

Although underrepresentation of elderly people in medical research (and its consequence, limited representativeness of research findings) was discovered decades ago, it is still present in rheumatology trials (1). Exclusion criteria based on age, organ function, and physical or cognitive performance criteria add to this problem (1).

Researchers usually do not justify their exclusion criteria (1,9,10). Possible reasons include fear of increased adverse event

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(AE) rates and reduced participant retention as a consequence of including elderly in trials. Attrition decreases statistical power and may introduce bias, and both reasons may complicate analysis.

RA and OA are major contributors to global disability and common rheumatic diseases, and both are known to occur predominantly in elderly people (1,11–16). We decided to investigate whether in RA and OA trials inclusion of higher proportions of elderly people leads to lower retention (even after adjusting for potential meta-confounders), and, if present, whether such an association is connected to attrition due to AEs or lack of efficacy (LoE).

MATERIALS AND METHODS

This study is part of the Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis (GLORIA) project and trial (http://www.gloriatrial.org/) (17). It conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (for the PRISMA checklist, see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24051/abstract) (18). The prespecified protocol (see Supplementary Appendix A) was preregistered with the protocol registry protocols.io (https://dx.doi.org/10.17504/protocols.io.uhaet2e).

Search strategy. The online biomedical database Medline (via PubMed) was searched for randomized controlled trials (RCTs) in RA or OA of any intervention published in 2016 or 2017. Additionally, a hand search of major RA and OA reviews and guidelines was conducted. Exact search strings can be found in the study protocol (see Supplementary Appendix A, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24051/abstract).

Eligibility criteria. Trials had to report a measure of central tendency for age as either the mean or median age of their baseline populations (i.e., not only of participants who completed studies). Publications in languages other than English, French, Spanish, German, Italian, Hungarian, Portuguese, Dutch, Slovakian,

and Romanian were excluded to correspond to the skills of participating GLORIA collaborators, as were trials in pediatric populations. Two authors (AP and TB) independently selected the studies for inclusion, first removing duplicates, then screening the publications by title and abstract, and finally reading full articles. They achieved consensus by discussion when necessary. For additional specifications, see our study protocol (see Supplementary Appendix A, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24051/abstract). Formal screening of search results against eligibility criteria has already been performed for a previous study (1). For the current study, all trials reporting data on retention were included.

Data collection, management, and preparation. Data were extracted into predefined Excel 2016 (Microsoft Corporation) spreadsheets that were derived from the Cochrane Collaboration's recommendations but modified for our purposes (19). Information on the type of intervention was categorized into "pharmacological," "surgical," "psychological," and "physical/physiotherapeutic." Information on the type of funding was categorized into "industry funding present" and "no industry funding present." The proportion of included elderly individuals (PE) ("elderly" being defined by an age of ≥65 years) was directly extracted where possible and otherwise estimated. Estimation was performed according to an established model that assumes that age approximately follows normal distribution (1,20,21). Models included a truncation at a lower limit of age 18 years (if not reported otherwise) and an upper age limit if such a limit was imposed by the respective study. Additional details can be found in our study protocol (see Supplementary Appendix A, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24051/abstract).

Risk of bias. No risk of bias assessment was performed. The sole outcome (dependent variable) of this study was participant retention (and not a traditional risk or benefit outcome of a specific intervention). This allowed the inclusion of a high number of studies while retaining feasibility.

Data synthesis. All analyses were conducted in R, version 3.5.1 (R Foundation) using the package metafor (22). Restricted maximum likelihood, mixed-effects, meta-regression models were constructed to assess whether PE is independently associated with participant retention (23). The following trial-level features were considered potential covariates (apart from PE): study duration, condition (RA or OA), type of intervention, region, sample size, and the proportion of women. A relevant study-level covariate was defined as one that significantly decreases the between-study variance, estimated as T^2 (an estimate for tau squared) as a consequence of inclusion in the mixed-effects meta-regression model. We used additional sensitivity analyses to assess whether associations were connected to a specific type of attrition, i.e., attrition due to AE or LoE. Analyses allowing

for first-order interactions (PE × study duration and PE × type of intervention) and an analysis comparing retention in trials employing upper age limits versus those without upper age limits were conducted on a post hoc level.

Retention as the dependent variable was coded into a simple proportional effect size and then logit transformed. The logit transformation was used to form an unbounded (in contrast to the 0 to 1 bounded nature of proportions) and normally distributed estimate to facilitate meta-regression. For retention rates of 1.0, a count of 0.5 was added to the number of participants completing and not completing the trial in order to include these in the meta-analysis (i.e., prior to the logit transformation) as well as to calculate 95% confidence intervals (95% CIs) for individual studies for the forest plot. After analysis, logit units were back transformed to proportions and converted to percentages for the purpose of reporting. Heterogeneity was measured and interpreted with the I^2 inconsistency index (19). The 2-sided significance level α was set at 0.05.

RESULTS

Search results and study characteristics. The search yielded 789 results (Figure 1). Of these, 243 RCTs were deemed eligible (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24051/abstract, for a list of all included studies). RCTs included a total of >48,000 participants (29,000 with RA and 19,000 with OA) (Table 1). The majority of RCTs were conducted in Europe and Asia, although most RA trials were not limited to a single region. Industry funding was present in most RCTs in RA (68%), in contrast to RCTs in OA (23%). Generally, OA trials included more elderly and more female participants and had smaller sample sizes per trial. Only 2 trials mentioned any kind of strategy to facilitate inclusion of elderly people, both concerning the recruitment of participants.

Retention and sensitivity analyses. Pooled trial retention (random-effects) across all trials was 88% (95% CI 87%, 90%; I^2 90%) (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24051/abstract). No significant association between PE and participant retention was found in the unadjusted model (slope β = 0.00 [95% CI –0.01, 0.01], P = 0.966) (Figure 2) or any other adjusted model (Table 2 and Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24051/abstract). Of all included covariates, only study duration (longer study duration associated with reduced retention; slope β = –0.004 [95% CI –0.005, –0.002], P < 0.001) and the type of intervention (surgical interventions averaging the highest retention [94%], and psychological interventions averaging the lowest retention [82%]; P < 0.001) were associated with retention (see Supplementary
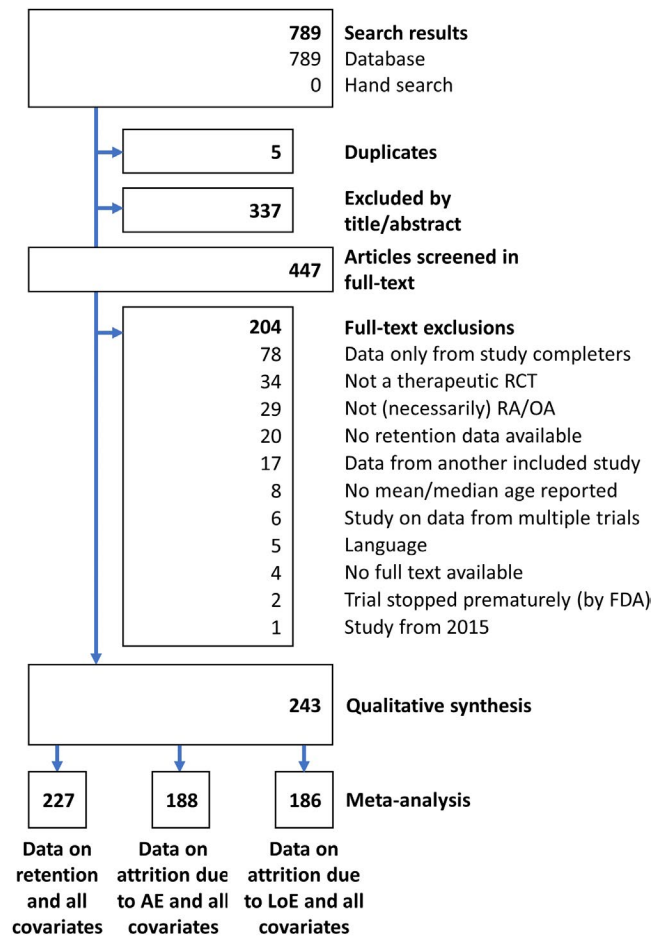

Figure 1. Search flow. Searches were performed January 19, 2018. A total of 243 trials were used for the forest plot of retention, 227 trials for meta-regression models for retention, 188 trials for meta-regression models for attrition due to adverse events (AE), and 186 trials for meta-regression models for attrition due to lack of efficacy (LoE). RCT = randomized controlled trial; RA = rheumatoid arthritis; OA = osteoarthritis; FDA = Food and Drug Administration.

Table 2 and Supplementary Figure 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24051/abstract).

Post hoc analyses allowing for first-order interactions of PE × type of intervention revealed small but statistically significant associations between PE and retention for some interventions. Retention increased with PE in pharmacologic trials (slope β = 0.01 [95% CI 0.00, 0.02]) but decreased in physical/physiotherapeutic trials (slope β = –0.01 [95% CI –0.02, –0.00], overall P for interaction = 0.05) (see Supplementary Table 3 and Supplementary Figure 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24051/abstract). Further post hoc analyses allowing for first-order interactions of PE × study duration did not yield a significant association between PE and retention (slope β = 0.00 [95% CI –0.00, 0.00], P for interaction = 0.946) (see Supplementary Table 3). Comparing trials that did employ upper age limits with those that did not yielded a statistically significant difference in retention of 3.3 percentage points (P = 0.011) (see Supplementary Table 4,

Table 1. Study characteristics*

	OA (n = 147)	RA (n = 96)	P†
Region			<0.001
Africa	3 (2)	1 (1)	
Asia	38 (26)	21 (22)	
Central and South America	6 (4)	2 (2)	
Europe	60 (41)	27 (28)	
Multiple regions	1 (1)	42 (44)	
North America	23 (16)	2 (2)	
Oceania	16 (11)	1 (1)	
Intervention			<0.001
Other	28 (19)	4 (4)	
Pharmacologic	35 (24)	79 (82)	
Receiving biologic agents‡	1 (3)	56 (71)	
Receiving biosimilars§	0 (0)	9 (16)	
Physical therapy	47 (32)	9 (9)	
Psychological	5 (3)	4 (4)	
Surgical	32 (22)	0 (0)	
Funding			<0.001
Any industry funding	34 (23)	65 (68)	
No industry funding	96 (65)	28 (29)	
Not available¶	17 (12)	3 (3)	
Sample size, median (IQR)	86 (49–162)	221 (90–392)	<0.001
Study duration, median (IQR) weeks	24 (8–52)	25 (15–52)	0.120
Proportion elderly, median (IQR)	0.46 (0.31–0.64)	0.17 (0.10–0.22)	<0.001
Proportion female, median (IQR)	0.65 (0.55–0.77)	0.81 (0.77–0.85)	<0.001
Mean age, median (IQR) years	63 (60–67)	53 (51–55)	<0.001
Upper age limit present			0.267
Yes	54 (37)	28 (29)	
No	93 (63)	68 (71)	

* Values are the number (%) unless indicated otherwise. OA = osteoarthritis; RA = rheumatoid arthritis; IQR = interquartile range.
† P values were obtained from the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.
‡ Percentages are based on all studies on pharmacologic agents in the respective disease.
§ Percentages are based on all studies on biologic agents in the respective disease.
¶ E.g., no funding and conflicts of interest statement.

available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24051/abstract). PE was not significantly associated with attrition due to AE or LoE in any model (see Supplementary Figures 4 and 5, and Supplementary Tables 5 and 6).

DISCUSSION

Our study shows that retention in RA and OA trials is very high and virtually unaffected by the proportion of elderly individuals enrolled. In a previous study, we found the findings of current RCTs in RA and OA to lack applicability to the elderly population due to significant underrepresentation compared to real-world settings (1). This underrepresentation is caused by a multitude of factors. Reasons include patient-level (e.g., elderly people may experience reduced mobility or encounter difficulties when judging benefits and risks), physician-level (e.g., physicians fearing toxicity issues in elderly people), but mainly trial-level exclusion criteria (1,24–26). Often, exclusion criteria are applied to create a relatively healthy trial population (apart from the disease under study) to allow a clean assessment of the effect of intervention. Unfortunately, most are related to higher age, such as comorbidities,

organ dysfunction, cognitive impairment, physical disability, and polypharmacy (9,27). Chronological age itself continues to be an independent exclusion criterion for study participation, which compounds the problem (1,9,28). Because study authors rarely justify this separate age criterion (1,9,10), we can only speculate about further reasons. Older adults may have limited life expectancy, which might not allow them to complete studies to the final follow-up, and AEs might occur more frequently in elderly people, consequently deteriorating risk–benefit ratios (1,9,27). Fear of reduced trial retention might add to this (1,29,30).

Previous studies on retention have not come to a consistent result. A review of population-based studies found higher age to be a predictor for dropping out, as did a longitudinal study on aging (29,31). Quite the contrary, younger age was found to be associated with attrition in a population-based study on prostate cancer and in a randomized trial on weight loss and hypertension management (30,32). The only rheumatologic study that we could locate evaluated retention in an RA registry; here, those who dropped out were not found to be older than those still participating after 5 years of follow-up (33). Our study confirms this latter finding for RCTs in RA and OA.
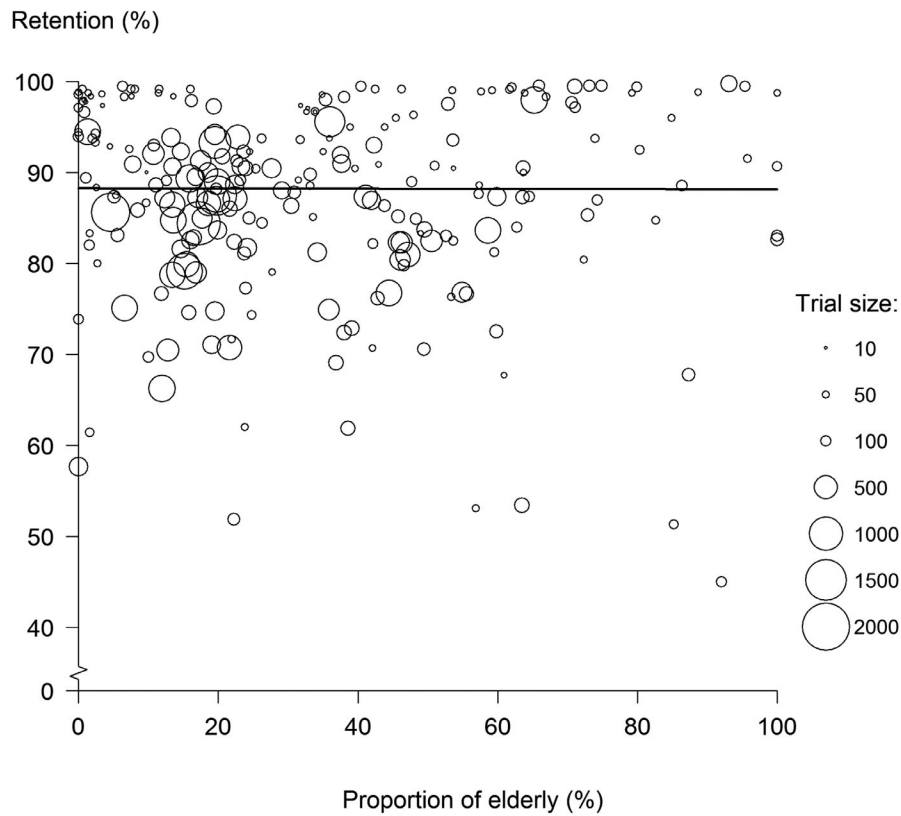
Figure 2. Bubble plot of trial retention against proportion of elderly people. The size of each bubble is proportional to the number of participants. The solid line illustrates the restricted maximum likelihood–based random-effects meta-regression of the logit-transformed retention, with proportion of elderly people as study-level covariate (n = 227 trials), slope β = –0.0001 (95% CI –0.0050, 0.0048), P = 0.966. Slope β should be interpreted as the increase in the logit(retention) per % increase in elderly people.

To further validate our results, we conducted several post hoc analyses, some of which were suggested during peer review. Analyses allowing for interaction showed a small decrease in retention in the proportion of elderly patients in physical/ physiotherapeutic trials, possibly owing to the strenuousness of such interventions. In contrast, retention showed a small increase in the number of elderly patients in pharmacologic trials. The reason for this observation is unknown; but a possible

Table 2. Meta-regression analyses for the association between the logit-transformed trial retention and proportion of elderly people (n = 227 trials)*

Model	Slope β for % elderly	95% CI	tau^2	$\%tau^2_{explained}$†	I^2	P for % elderly‡
Unadjusted§	–0.00	(–0.01, 0.01)	0.62	–	93.6	0.97
Adj. for study duration	0.00	(–0.00, 0.01)	0.54	12.9%	92.7	0.90
Adj. for disease	–0.01	(–0.01, 0.00)	0.63	–1.2%	93.7	0.14
Adj. for intervention	–0.00	(–0.01, 0.00)	0.61	2.1%	93.4	0.58
Adj. for region	0.00	(–0.01, 0.01)	0.63	–1.2%	93.6	0.71
Adj. for number of patients	–0.00	(–0.01, 0.00)	0.63	–1.9%	93.6	0.58
Adj. for proportion of females	–0.00	(–0.01, 0.01)	0.63	–0.9%	93.6	0.83
Adj. for study duration and intervention¶	–0.00	(–0.01, 0.00)	0.42	32.0%	90.7	0.47

* Estimates from multivariable restricted maximum likelihood–based meta-regressions for the association between retention (number of participants completing a trial divided by the number of randomized participants) calculated via a logit transformation and proportion of elderly individuals. Slope β should be interpreted as the increase in the logit(retention) per % increase in the proportion of elderly individuals. 95% CI = 95% confidence interval; adj. = adjustment.
† $\%tau^2_{explained}$ was calculated as ($tau^2_{adjusted\ model}$ – $tau^2_{unadjusted\ model}$)/$tau^2_{unadjusted\ model}$ × 100.
‡ P value is from a Wald's test for the effect of the proportion of elderly individuals in the model.
§ The unadjusted model includes only the proportion of elderly individuals as covariate and, hence, provides an unadjusted estimate for the slope for proportion of elderly individuals.
¶ Further adjustments were made by including all variables in the same model that were shown to decrease tau^2 as a consequence of inclusion in a model (in addition to proportions of elderly individuals).

explanation might be that there usually is closer monitoring in this kind of study, to which elderly individuals might respond especially well. Furthermore, we found that the reduction of retention seen in trials with longer duration did not worsen with more elderly patients being included, indicating that elderly patients might finish studies as reliably as younger ones even if trials are of longer duration. In a final post hoc analysis, studies employing upper age limits were shown to perform slightly better in terms of retention. However, this difference was marginal and does not detract from our overall finding that there is no clinically relevant association between PE and retention.

While PE was not associated with participant retention, 2 other contextual factors were study duration and the type of intervention. Expectedly, trials with longer study duration showed decreased retention. Furthermore, surgical trials averaged the greatest retention, and psychological trials averaged the least retention compared to other interventions ("other," pharmacologic, and physical/physiotherapeutic interventions ranking in between, respectively). This may be related to the direct implications of an intervention in regard to participants: patients are closely bound to further care and consequently to study teams the more invasive an intervention is. We also found PE not to be associated with attrition of a specific type, i.e., due to AE or LoE. This finding should, however, not be misinterpreted to mean that elderly people generally experience similar rates of AE or LoE compared to their younger counterparts.

To our knowledge, this is the first study to analyze age and other contextual factors as predictors of retention in rheumatology trials on a meta-analytical level. Strengths of this study comprise protocolized execution including analyses with adjustment for potential confounders, a substantial number of trials and participants, and a systematic literature search not limited to the English language. Study selection was performed by 2 authors (AP and TB) to decrease the risk of systematic bias.

Still, the current study does have limitations. The search was limited to Medline. However, including trials indexed elsewhere only should not significantly influence our results, and Medline is said to be the most important biomedical database currently (34). Furthermore, PE had to be estimated in most cases. Yet, our study's method of estimation is established and has been applied several times in peer-reviewed research (1,20,21). Another limitation is the possibility of what is called "ecological bias" (23). Ecological bias in this case means that the relationship between age and dropping out of a study might not be the same when we look at summary measures (i.e., retention and PE) across trials versus looking at the relationship between age and dropping out within each study.

Another limitation of our study is that the elderly patients who were analyzed in our study belong to selected elderly populations. They differ from the general elderly population by selection mechanisms introduced by, e.g., exclusion criteria such as comorbidities. Therefore, in trials including real-world elderly

patients, PE might be associated with retention. Yet, our results are in line with those from an RA registry that indeed included real-world patients (33). As there is no other evidence concerning elderly patients and retention in rheumatology, further research is warranted. Data from the currently running GLORIA trial, which explicitly includes real-world elderly RA patients, might eventually shed a brighter light on this issue (17).

Furthermore, overall heterogeneity regarding retention was considerable, with an inconsistency (I^2) of 90%. However, this was to be expected since we applied simple eligibility criteria resulting in a heterogeneous study population (with variable trial design, population, and intervention).

In conclusion, retention in RA and OA trials is high and virtually unaffected by the proportion of elderly people enrolled. This finding should encourage clinical investigators in rheumatology to include more elderly people and lead to study populations more representative of real-world patients, with the downstream consequence of more applicable research being available to the end user.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Palmowski had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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