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Original Research Article

Assessment of the impact of age on DIBH in radiotherapy based on the prospective GATTUM and B-REST trials

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ABSTRACT

Background: Adjuvant radiotherapy (RT) of left sided breast cancer is increasingly performed in deep inspiration breath hold (DIBH). This technique requires active involvement and compliance of patients as well as pulmonary endurance. Since previous studies focused on female patients with a median age under 65 years to test practicability of DIBH and advantages in comparison to free breathing (FB), DIBH in elderly patients over 65 years remains mostly underexplored. This study aims to evaluate attitudes and feasibility of DIBH in elderly breast cancer patients.

Methods: First a 14-item survey of 100 female breast cancer patients aged ≥65 years was conducted to assess their attitudes toward DIBH and their breath-hold capability. Secondly, we performed a matched-pair analyses using pooled data from the prospective GATTUM and B-REST trials to compare respiratory and dosimetric parameters during DIBH between patients aged ≥65 years (n = 30) and <65 years (n = 30).

Results: According to the survey large majority of patients were interested in DIBH: 98 % stated that age should not be a criterion when selecting patients for DIBH, and 66 were able to hold their breath > 20 s. Based on the matched-pair analyses of the GATTUM and B-Rest trials, no significant differences were observed regarding breath hold amplitude, duration and stability, and in DIBH-induced dose reduction to organs at risk between elderly (≥65) (n = 30) and younger patients (n = 30).

Conclusion: Based on our results age alone should not be used as a criterion for excluding patients from DIBH in the treatment of left-sided breast cancer.

Introduction

Radiotherapy (RT) is rapidly evolving as the standard of care in adjuvant treatment following breast conserving surgery in patients with left sided breast cancer (1,2). RT is administered using deep inspiration breath hold (DIBH) to minimize cardiac dose exposure (3–6) and therefore reduce the likelihood of known cardiac morbidity and mortality (7,8). DIBH requires both active participation and compliance, as well as the ability to reproducibly hold the breath for a defined duration (9,10).

While the benefits and feasibility of DIBH have been well-documented in younger populations, particularly those under 65 years of age, older patients are often underrepresented in such studies (11). In a recently published study investigating surface-based DIBH in left sided

Abbreviations: CT, computed tomography; DIBH, deep inspiration breath hold; FB, free breathing; Heart Dmean, mean dose to the heart; LAD Dmean, mean dose to the left anterior descending coronary artery; Lung V18, the volume of the left lung receiving at least 18 Gy; R&R, respiratory training program combined with relaxation training; RT, radiotherapy.

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breast cancer the participants had a mean age of 57 years (12). Similar in a study by Jacobson et al., and in the UK HeartSpare Study mean age was 56 years and 56 years, respectively (13,14). To our knowledge none of the studies provide a subgroup analysis for elderly patients.

The lack of data for elderly patients is critical given that the median age at breast cancer diagnosis is 63 years and a large proportion of patients is > 65 years old (15). This raises important questions about the applicability of DIBH in elderly patients, especially given the physiological changes associated with aging, such as reduced lung capacity, decreased breath holding ability and potential comorbidities. At the same time it is also known that older patients have a higher baseline risk of cardiac morbidity and mortality, making the reduction of cardiac radiation exposure particularly critical, not only to maintain health during cancer survivorship, reduce health care costs but also to improve the quality of life of older breast cancer patients. Understanding age-specific barriers and opportunities will help optimize DIBH protocols and improve access to this cardioprotective technique across all age groups.

The current study aimed to address this gap by investigating the perception about DIBH in female breast cancer patients over 65 years and to examine their capability to perform DIBH as well as the dosimetric success of DIBH in elderly compared to younger patients.

Methods

The work was conducted as two sub-studies of the prospective GATTUM and B-Rest Trials at the Department of Radiation Oncology, Technical University of Munich, Germany, from October 2015 to July 2024.

Since 2015 patients undergoing DIBH were included in prospective trials at our center – until 2021 patients were enrolled in the GATTUM trial and from 2022 on patients were enrolled in the subsequent B-Rest trial. While both studies focus on the optimization of DIBH, the studies have different primary objectives:

The prospective GATTUM trial (NCT03534570) was conducted to identify predictive metrics enabling the estimation of heart dose reduction achieved through DIBH in comparison to FB in patients with left sided breast cancer undergoing RT, thereby facilitating precise patient selection. Secondary endpoints include quality of life and cosmetic outcomes (16). The objective of the prospective clinical B-REST trial (NCT05975190) is to enhance patient compliance and performance of DIBH, thereby further reducing cardiac dose during left breast irradiation. For this, the randomized trial evaluates the benefit of an active and structured pre-treatment respiratory training program combined with relaxation training for breast cancer patients undergoing adjuvant radiotherapy for left-sided breast cancer (17).

Patient survey study

As part of the B-REST project we conducted a prospective, pseudonymized *patient survey study*, consisting of a one-time paper-based questionnaire administered to female breast cancer patients treated in our department to explore their attitudes towards DIBH in the RT process. Patients aged 65 years or older were enrolled into the survey study between March and July 2024 in the Department of Radiation Oncology at the Technical University of Munich. The inclusion criteria mandated proficiency in German language and the physical and mental capability to complete a structured questionnaire. All suitable patients in this subproject (≥65 years with breast cancer, undergoing radiotherapy or with radiotherapy in their medical history) were approached at the outpatient department and a response rate of 97 % was achieved. All patients received the same written information about DIBH in the informed consent form prior to the patient survey. Patients completed the questionnaire independently but could ask a research staff member for clarification at any time if questions arose.

The questionnaire was developed in collaboration with experts in oncology and radiation oncology to capture the patients' willingness and attitude toward RT in DIBH. The structured questionnaire consisted of 14 questions: 5 questions concerning age and radiation treatment history, 9 questions about attitudes towards active participation in RT and DIBH, and one question on willingness to trial participation. All but the initial 5 questions used a four-point Likert scale (Supplemental Material Questionnaire 1, Table 1). The results are presented as follows: "yes" for "applies" and "mostly applies," and "no" for "does not apply" and "mostly does not apply."

In addition to the questionnaire, the patients' maximal breath holding duration was measured at the time of the survey. For this procedure, patients were instructed to hold their breath for as long as possible. The duration was measured from the end of the inhalation to the onset of exhalation.

Descriptive statistics were employed to summarize patient demographics and questionnaire responses.

Responses to individual questionnaire items were expressed as percentages.

Age group comparison study

In a second step, we performed a pooled retrospective subgroup analysis of patients that had been included in the prospective GATTUM and B-REST trials (October 2015 – July 2024). The goals of this study were to investigate differences in respiratory performance parameters (DIBH duration and stability), and degree of cardiac and lung dose reduction during DIBH between elderly (≥65 years) and younger patients. From 241 study patients, we included all evaluable 30 patients aged ≥65 years in this analysis. A comparison cohort of 30 patients aged <65 years was matched based on comorbidities: primary systemic therapy, cardiac/pulmonary disease, smoking status and alcohol consumption. These criteria were selected due to their impact on cardiac

Table 1
Patients interest and willingness concerning DIBH in RT.

Questions	Breast cancer patients ≥65 years (n = 100)	
	Yes, n (%)	No, n (%)
I have previously received radiation to the breast in my lifetime	82 (82)	18 (18)
I have previously received radiation in deep inspiration breath hold in my lifetime	23 (23)	77 (77)
Active participation during radiation therapy is important to me	88 (88)	12 (12)
I find the topic of radiation therapy in deep inspiration breath hold interesting and would like to be informed about it as part of a therapy	81 (81)	19 (19)
By actively participating during radiation therapy, I would feel more involved in the therapy	83 (83)	17 (17)
I would feel capable of holding my breath for 20–30 s if requested during the therapy	88 (88)	12 (12)
I find the idea of holding my breath for several seconds (approximately 20–30 s) during radiation therapy stressful	14 (14)	86 (86)
If I were required to hold my breath during radiation therapy, I would find pre-training useful	57 (57)	43 (43)
I would take time for training on holding my breath	54 (54)	46 (46)
Age should not be used as the sole criterion for patient selection when deep inspiration breath hold is offered for improved sparing of organs at risk	98 (98)	2 (2)
In your opinion, can DIBH help to protect the heart?	100 (100)	0 (0)
Would you be willing to participate in a study on the feasibility of deep inspiration breath hold during radiation therapy	79 (79)	21 (21)
	Median duration in seconds	
Result of the DIBH (breath holding)	23.8	

DIBH: Deep Inspiration Breath Hold; RT: Radiotherapy.

and pulmonary function.

Respiratory curves obtained from planning computed tomography (CT) scans were analysed for breath hold duration (measured from the end of the inhalation to the onset of exhalation in seconds), breathing amplitude (defined as vertical deviation between breathing baseline and deepest breath hold), stability of breath holding (defined as vertical deviation between maximum inhalation in the beginning of breath hold and minimum inhalation after losing inhaled air). The breath hold was stopped at the conclusion of the planning CT scan and therefore does not reflect the duration of actual achievable breath hold duration. Additionally, the DIBH induced reduction in heart and lung radiation dose (over free breathing) was assessed, including delta (FB-DIBH) of the mean dose to the heart (heart Dmean), the delta (FB-DIBH) of the mean dose to the left anterior descending coronary artery (LAD Dmean), the delta (FB-DIBH) of the volume of the left lung receiving at least 18 Gy (V18), and the delta of the radiation dose to the contralateral (opposite) breast.

Differences between groups for categorical variables were assessed using chi-square tests. For continuous variables, appropriate statistical tests were chosen based on data distribution: the Mann-Whitney *U* test for independent non-normally distributed data, the Wilcoxon Signed-Rank test for paired non-normally distributed data, and independent t-tests for normally distributed data. All analyses were performed using GraphPad Prism software (version 10.2.3). Results were considered statistically significant at $p < 0.05$.

The specific studies were approved by the local institutional review board (304/15 S, 2020-277_2-S-NP, 2024–48-S-CB), and all participants provided written informed consent.

This analysis is part of the prospective B-REST project, which is supported by the *Deutsche Krebshilfe* (German Cancer Aid).

Results

Patient survey study

A total of 100 breast cancer patients (of 103 invited patients) responded to the patient survey. All patients were female with a median age of 74 years (range 65–87 years).

Most patients (88 %) recognized the importance of active participation during RT, and 81 % expressed interest in undergoing RT in DIBH, emphasizing the need for more information about the technique. Most importantly, 98 % of patients stated that age should not be a criterion for selection of DIBH (Table 1). Additionally, 83 % believed that active collaboration could enhance their participation in therapy. Confidence in breath holding ability was high, with 88 % of patients convinced they could hold their breath for 20–30 s, and only 14 % finding the task stressful. These findings suggest that elderly breast cancer patients were receptive to using DIBH in RT, with a strong interest in its potential benefits and confidence in their ability to perform the required techniques, though perceptions of training utility vary. 23 % of patients of the survey had undergone DIBH with explanation and training, but all participants were informed about DIBH with a short paragraph in the survey. However, separate analyses of those patients who underwent DIBH before and those who did not know about this technique, showed no relevant differences between these groups (Supplemental Table 2).

Participating patients in our study aged 65 years and older were able to hold their breath for a median duration of 23.8 s. For patients over 80 years, a median breath hold of 21.2 s was measured.

Age group comparison study

DIBH ability in elderly (≥65 years) patients in comparison to younger patients (<65 years)

Patients' characteristics are shown in Table 2. The age group analysis of GATTUM and B-REST trial patients comparing DIBH ability and dose reduction is presented in Fig. 1. The breathing amplitude of patients ≥65 years was not significantly different from that of patients <65 years. Similarly, the stability of breath holding (median of 0.3 cm) was similar between the two groups. Patients in both age categories were able to maintain breath hold duration for the requirement of the planning CT scan (breath hold was stopped after the duration of the planning CT scan), showing likely longer median duration of 16 s for those over 65 vs. 14 s for those under 65 years ($p = 0.02$). Since breath hold

Table 2
Patients' characteristics of the age group comparison study.

	n	%
primary systemic therapy		
yes	10	16.6
no	50	83.3
cardiac/pulmonary disease		
yes	25	41.6
no	35	58.3
smoking status		
yes	12	20
no	48	80
Alcohol consumption		
yes	10	16.6
no	50	83.3

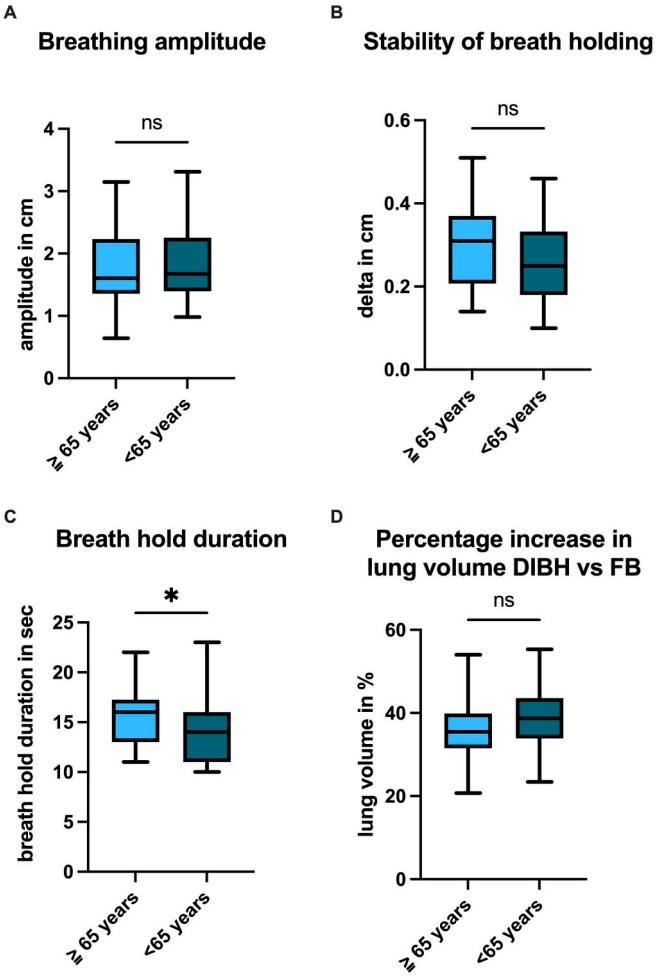

Fig. 1. DIBH Dosimetry and Respiratory Curve Analysis in the age group comparison study of DIBH ability in elderly (≥65 years) vs. younger patients (<65 years) in the GATTUM and B-Rest Trials. A: Breathing amplitude. B: Stability of breath holding. C: Breath hold duration. D: Percentage increase in lung volume. The difference in breath hold duration is the only statistically significant difference ($p = 0.02$). ns = not significant; * = significant.

duration was terminated at the conclusion of the planning CT scan, the statistically significant difference may represent a random occurrence. However, the inhaled volume during DIBH (delta total lung DIBH-FB) was slightly higher in younger patients (1777.5 l vs. 1571.0 l) (Supplemental Table 1 and Fig. 1).

Age group comparisons of dosimetric parameters are presented in Table 3. The DIBH-induced dose reduction of heart Dmean in patients ≥65 years of age, with a mean of 0.7 Gy was similar to that of patients under 65 years (0.7 Gy). The DIBH-induced dose reduction of LAD Dmean was slightly higher in younger patients (4.6 Gy vs. 2.6 Gy). While this gain of 4.6 Gy dose reduction was numerically substantial in younger women vs. women ≥65 years, it did not reach statistical significance (p = 0.06). Neither did the DIBH-induced dose reduction of V18 of the left lung. These findings suggest minimal differences in dosimetric outcomes across age groups, with perhaps a trend towards slightly greater DIBH-induced dose reductions of LAD Dmean observed in younger patients.

Discussion

To our knowledge, this study is the first to specifically address the ability of older breast cancer patients to successfully perform DIBH. Our patient survey study demonstrated that elderly breast cancer patients (≥65 years) exhibit a strong interest in and capability for performing DIBH during RT. A majority expressed willingness to participate in DIBH, with 98 % believing age should not limit its use, and 66 % achieving breath hold durations exceeding 20 s. Our age group comparison study of dosimetric outcomes between patients aged ≥65 and <65 years showed no significant differences in the dosimetric improvement of heart and lung sparing from DIBH, affirming its feasibility in older patients. These findings challenge the current practice of underrepresenting elderly patients in DIBH protocols and suggest its broader applicability.

Our results strongly encourage to offer DIBH irrespectively of age for the following reasons:

1) High interest of DIBH irrespectively of age.

Our patient survey results demonstrate a high level of acceptance of DIBH among patients aged 65 years and older. Over three-quarters expressed interest in and willingness to undergo RT in DIBH, and more than three-quarters were confident in their ability to hold their breath for 20 to 30 s. This patient perception of their own breath holding ability was parallelled by their actual ability to breath hold for a median of 23.8 s. A study by Beaton et al. (18) involving 30 patients similarly reported high acceptance of DIBH in a patient experience questionnaire; however, the cohorts' mean age of 54 years was much younger than in that of our study. In a study by Dower et al. (19), 22 patients with a median age of 64 years were asked about their experience with DIBH and reported positive treatment experiences when they felt relaxed, pain-free, and in control of their treatment. The results of our cohort with a mean age of 74 years (range: 65 to 87 years) expands the positive experience with DIBH reported by Beaton et al. and Dower et al. to older patient groups.

2) Satisfactory capability of DIBH in elderly patients.

As shown in the age group comparison study, patients ≥65 years were equally capable of holding their breath during the planning CT as those under 65 years. Their breathing amplitude, breath hold duration and stability of breath holding in DIBH as well as the inhaled volume during DIBH (delta total lung DIBH-FB) were not inferior to those of patients under 65 years.

To our knowledge, no data exists regarding the feasibility of DIBH in elderly patients with a median age over 65 years. Ahmad et al. sought to develop a predictive model for DIBH eligibility, identifying both increased average breath hold duration and reduced amplitude as significant predictors. Notably, advanced age was associated with a higher likelihood of ineligibility for DIBH. However, it is important to note that the patient cohort in Ahmad et al.'s study had a limited age range of 42 to 59 years (20). A study by Ledsom et al. found no correlation between patient age and the amplitude ratio increase during DIBH. However, patients had a mean age of 48 years (range 35–63 years) (11). Although the SAVE-HEART study included 40 % of patients over the age of 60, no subgroup analysis was conducted to compare their DIBH performance with that of younger patients (12). Our study therefore fills an important knowledge gap on patients' ability of DIBH performance that is readily translatable to clinical practice.

3) Similar dosimetric improvements with DIBH for heart and lung sparing in elderly patients.

However, even with adequate patient willingness and DIBH performance the measure of success for DIBH is the actual dosimetric improvement of heart and lung sparing. Our age comparison study shows that this is achievable in elderly patients. The reductions in heart Dmean, LAD Dmean and V18 of the lung with DIBH compared to FB were similar in patients both ≥65 and <65 years of age. Given that older patients have a higher baseline risk for cardiac events, it is crucial to offer these patients the best cardiac sparing possible. This is particularly important because breast cancer is a disease prevalent in older populations and the breast cancer population continues to age due to better treatment. A study by Simonetto et al. demonstrated that DIBH can reduce the mean expected years of life lost, especially in patients with a high cardiopulmonary baseline risk, a favorable tumor prognosis, and a high mean heart dose during FB. Notably, the reduction in mean expected years of life lost was independent of patient age in those with a good tumor prognosis (21). This age independence of the clinical DIBH benefit underscores our study's conclusion that DIBH should be equally offered to elderly as to younger patients.

Table 3
DIBH-induced improvements in dosimetry parameters for heart, lungs and contralateral breast comparing patients of ≥65 years and <65 years old.

	Age	Mean	SD	P value
Delta (FB-DIBH) in Heart Dmean	≥65 years	0.7 Gy	0.8 Gy	1.0
	<65 years	0.7 Gy	0.7 Gy	
Delta (FB-DIBH) in LAD Dmean	≥65 years	2.6 Gy	4.4 Gy	0.06
	<65 years	4.6 Gy	3.2 Gy	
Delta (FB-DIBH) in left lung V18	≥65 years	1.3 cm^3	2.9 cm^3	0.4
	<65 years	2.3 cm^3	4.3 cm^3	
Delta (FB-DIBH) in Contralateral mamma	≥65 years	0.0 Gy	−0.1 Gy	0.2
	<65 years	0.1 Gy	0.23 Gy	

Delta (FB-DIBH): Difference between free breathing (FB) and deep inspiration breath hold (DIBH);
Dmean: Mean Dose; LAD: Left Anterior Descending Coronary Artery; V18: Volume of the left lung receiving ≥18 Gy; SD = standard deviation; ns = not significant.

Strengths and limitations

This work addresses a significant gap in the existing literature by focusing on the feasibility and benefits of DIBH in elderly breast cancer patients, a population often underrepresented in previous research. By combining subjective patient-reported attitudes and perceptions towards DIBH with objective patient performance and dosimetric analyses, the study provides a comprehensive evaluation of DIBH from both patient-centered perspectives and clinically measured parameters of DIBH feasibility. The high response rate of 97 % in the patient survey further enhances the robustness of the data, reflecting a strong level of engagement and interest among participants.

While our findings are promising, the study's single-center design and inclusion of relatively fit elderly patients may limit the generalizability of results to more diverse populations. The study design carries the typical limitations of a survey study, including response rate and conformity bias. The prospective patient survey study was part of the B-REST project and aimed to understand better the perception of elderly patients regarding DIBH. Differently from the randomized trial, this subproject had broader inclusion criteria ($\geq$ 65 years with breast cancer, undergoing radiotherapy or with radiotherapy in their medical history). Therefore, the patient's collective is relatively inhomogeneous with a potential bias in responses. A potential confounder could be the fact that 23 % of the patients in the patient survey study had prior experience with DIBH. However, separate analyses of patients who had previously undergone DIBH and those who were unfamiliar with this technique showed no relevant differences between these groups. As the breath hold was stopped at the conclusion of the planning CT scan and therefore does not reflect the duration of actual achievable breath hold duration, because one measurement is not relevant for the capacity to hold onés breath for the entire treatment session, but all sessions do, this represents a further limitation.

The patient numbers in the age group comparison study are small and despite our effort of risk-factor based matching may be prone to potential random effects. The comparison groups, which were derived from the B-REST and GATTUM trials, are subject to potential selection bias, as these trials include patients $\geq$65 years of age who were already deemed suitable for enrolment into a prospective trial and thus may not fully represent outcomes in patients who are treated in community centres.

It should be noted that DIBH involves greater effort for both patients and the medical team, as it requires a certain level of training. This results in technical and time-related demands and may delay clinical workflow. In addition to this the overall rate of side effects after whole breast irradiation with modern RT is low even in the breathing technique and some may argue that the limited life expectancy of elderly patients makes further reduction of late effects less relevant.

However, our results clearer indicate that patients over the age of 65 clearly desire best possible sparing of the organs at risk and that DIBH is a feasible technique for the large majority of patients. Even if a careful assessment regarding the DIBH is necessary considering both the advantages and the disadvantages based on our results, age alone should not be a general selection criterion for DIBH.

Also, the existing uncertainties regarding the actual clinical efficacy of DIBH techniques beyond dosimetric variations and histograms requires further investigation concerning clinical outcome in future studies.

Conclusion

This study establishes that age should not be a limiting factor in offering DIBH to breast cancer patients, highlighting elderly patients' willingness for DIBH, its feasibility and comparable dosimetric advantages across age groups. Implementing DIBH in routine care for elderly patients has the potential to significantly improve treatment outcomes while reducing cardiac risks.

The analysis is part of the prospective B-REST project, which is supported by the *Deutsche Krebshilfe* (German Cancer Aid).

Authors' contributions

1) Guarantor of integrity of the entire study – RM, KJB.
2) Study concepts and design – RM, LMB, KJB, NAM, SEC.
3) Literature research – RM, KJB.
4) Clinical studies – RM, LMB, STB, SK, JN, JMB, MD, MA, MND, MO.
5) Experimental studies/data analysis – N/A.
6) Statistical Analysis – RM, LMB, KJB.
7) Manuscript preparation – RM, NAM, JN, KJB.
8) Manuscript editing – RM, LMB, STB, SK, JN, JMB, MD, MA, MND, MO, NAM, SEC, KJB.

Consent for publication

Not applicable.

Availability of data and materials.

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The specific studies were approved by the local institutional review board (304/15 S, 2020-277_2-S-NP, 2024-48-S-CB), and all participants provided written informed consent. The procedures set out in this trial, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki (2008 Version of the Declaration of Helsinki, adopted at the 59th WMA General Assembly, Seoul, October 2008). The trial will be carried out in keeping with local legal and regulatory requirements.

Ethics approval

The specific studies were approved by the local institutional review board (304/15 S, 2020-277_2-S-NP, 2024-48-S-CB).

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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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Appendix A. Supplementary data

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