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One-Week Regimen for Post-Operative Regional Irradiation in Breast Cancer: The ARROW Trial Protocol

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One-Week Regimen for Post-Operative Regional Irradiation in Breast Cancer: The ARROW Trial Protocol

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Abstract

Introduction: Shortening the duration of postoperative radiotherapy (RT) for breast cancer while maintaining efficacy and safety has become a significant trend. The three-week regimen of 40–42.5 Gy in 15–16 fractions is now a preferred option in clinical practice. Following the publication of the 5-year outcomes from the Fast-Forward trial, interest in one-week regimens has surged, prompting the initiation of multiple studies. However, trials exploring the one-week regimen for regional nodal irradiation (RNI), especially involving internal mammary nodes (IMN), remain scarce. Additionally, the optimal fractionation scheme for tumor bed boost in the era of ultra-hypofractionated regimens is still debated. To address these gaps, we have initiated the ARROW trial to evaluate the feasibility of a one-week regimen for RNI of 26 Gy in five fractions, with optional sequential tumor bed boost of 10.4 Gy in two fractions. The findings from our trial are expected to extend the application of ultra-hypofractionated regimens to include sequential tumor bed boosts and RNI, pioneering its use in IMN irradiation.

Methods and Analysis: The ARROW trial is an open-label, single-arm, multi-center Phase II trial, encompassing four teaching hospitals in China. Enrolled patients will receive a total of 26 Gy in five fractions to ipsilateral whole breast/chest wall and regional regions, including supra/infraclavicular nodes, IMN, and any portion of the undissected axilla deemed at risk. A sequential tumor bed boost of 10.4 Gy in 2 fractions is at the discretion of the radiation oncologist. The sample size for the ARROW trial was 197 patients. Both Intensity-Modulated Radiation Therapy (IMRT) and proton therapy are permitted. The primary endpoint is acute radiation-induced toxicity, graded according to RTOG criteria and CTCAE version 3.0. Secondary endpoints include cosmetic outcomes for breast-conserving surgery, late radiation-induced toxicity, local-regional recurrence, distant metastasis, invasive tumor-free survival, overall survival, and quality of life assessment.

Ethics and dissemination: The trial has been approved by the Ethical Committee of

Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, as well as the ethical committees of each participating center have also been obtained. Research findings will be submitted for publication in peer-reviewed journals.

Trial registration:

ARROW trial: NCT04509648

Strengths and limitations of this study

- The ARROW trial evaluates the feasibility of a one-week regimen for RNI of 26 Gy in five fractions in China.
- A sequential tumor bed boost of 10.4 Gy in 2 fractions is used in the trial.
- Both Intensity-Modulated Radiation Therapy and proton therapy are permitted.
- One of the limitations is that this study does not stratify according to clinicopathological, subtype or gene information.
- One of the limitations is that this trial is a single-arm phase II trial. The safety profile of this ultra-hypofractionated whole breast irradiation and internal mammary nodal irradiation regimen will help us to initiate subsequent phase III randomized controlled trial.

Background

Breast cancer is the most prevalent malignant tumor among women [1]. Postoperative radiotherapy (RT) can significantly reduce recurrence risk and improve survival for patients undergoing breast-conserving surgery (BCS) or those at high-risk post-mastectomy [2-6]. However, the traditional 5-7 weeks RT regimen may reduce patient compliance and strain limited RT resources. The UK START trials identified an α/β value of approximately 3.5 Gy for breast cancer tissue, indicating that hypofractionated (HF) RT, with higher single-fraction doses, is more suitable for breast cancer [7].

In recent years, evidence from randomized trials and real-world studies has established the three-week regimen of 40-42.5 Gy in 15-16 fractions as the preferred option for whole breast irradiation (WBI) [7-13]. This practice has gradually expanded to include regional nodal irradiation (RNI) [14-17]. In a randomized trial with a median follow-up of 58.5 months, Wang et al [15] demonstrated that HF-RNI of 43·5 Gy with 2.67 Gy per fraction was non-inferior to the five-week regimen of 50 Gy with 2 Gy per fraction for locoregional control and adverse effects.

The Fast-Forward trial marked a pivotal advancement by condensing the RT regimen to one week for WBI using ultra-hypofractionation [18]. With a median follow-up of 71.5 months, this trial demonstrated that a one-week regimen of 26 Gy in five fractions was non-inferior in local control and normal tissue effects compared to the standard three-week regimen of 40 Gy in 15 fractions. However, this trial gave the tumor bed boost using conventional fraction, extending the overall RT duration to 2 or 2.5 weeks. The feasibility of ultra-hypofractionation in the tumor bed boost irradiation remains unknown. The Nodal Sub-Study of the Fast-Forward trial further explored the non-inferiority of the one-week regimen of RNI in patient-reported arm/hand swelling [19]. This study excluded patients with an indication of internal mammary nodal irradiation (IMNI) due to the perceived uncertainty of its value at the time of protocol design. With advancements in RT technology, there has been a significant reduction in heart and lung doses associated with IMNI, leading to increasing recognition of its benefits in recent years [2, 4-6, 20, 21]. However, limited data is available on the use

of a one-week regimen in IMNI.

To fill in these gaps, we initiated the ARROW trial to evaluate the feasibility of a one-week regimen for RNI of 26 Gy in five fractions for early breast cancer, with optional sequential tumor bed boost of 10.4 Gy in two fractions. The results from our trial are expected to confirm the feasibility of a one-week regimen and extend the use of ultra-hypofractionated regimens to include sequential tumor bed boosts and RNI, pioneering its application in IMNI.

Methods

Study Design

The ARROW trial is an open-label, single-arm, multi-center Phase II trial being conducted at four teaching hospitals in China. The primary objective is to assess the feasibility of a one-week regimen of 26 Gy in five fractions for early breast cancer patients. Both Intensity-Modulated Radiation Therapy (IMRT) and proton therapy are permitted. The primary endpoint is the incidence of Grade ≥ 2 acute radiation-induced toxicities at any time from the start of RT to 6 months after completion. Secondary endpoints include cosmetic outcomes for patients with BCS, late radiation-induced toxicity, local-regional recurrence, distant metastasis, invasive tumor-free survival, overall survival, and quality of life. The radiation-induced toxicity was graded using RTOG criteria and CTCAE version 3.0.

In the ARROW trial, participants receive 26 Gy in five fractions for the ipsilateral whole breast/chest wall and regional lymphatic regions, including supraclavicular and internal mammary nodes, and any portion of the undissected axilla deemed at risk (detailed in the supplemental protocol). A sequential tumor bed boost of 10.4 Gy in two fractions is delivered in patient with high risk factor, which is at the discretion of the radiation oncologist. **Figure 1** illustrates the study design of the trial. The ARROW trial (NCT04509648) is registered on ClinicalTrials.gov.

Participants and Recruitment

The clinical team will identify and approach eligible patients during their initial visit to the Department of Radiation Oncology, offering the opportunity for potential study participation. They are provided with a comprehensive overview of the study's objectives, procedures, benefits, and risks to thoroughly understand their involvement. Those who express interest, meet the inclusion criteria, and fully comprehend the study's implications will be invited to provide written informed consent. Following voluntary consent, participants will be officially enrolled in the study.

The first patient of the ARROW trial was enrolled on 21 January 2021.

Inclusion and Exclusion Criteria

Inclusion:

- Aged 18 years or older.
- Pathologically invasive breast cancer
- Undergoing BCS or mastectomy with reconstruction allowed, along with axillary lymph node dissection or sentinel lymph node biopsy.
- Axillary lymph node metastasis confirmed histologically (involving one or more nodes), or node-negative axilla with an indication for RNI as determined by the radiation oncologist.
- The surgical incision has completely healed, with no signs of infection.
- Negative surgical margin
- KPS ≥80 and life expectancy of more than 5 years.
- Estrogen-receptor, Progesterone-receptor, HER-2, and Ki67 index assessment on the primary breast tumor or axillary nodes is feasible.
- Provide written informed consent.
- Women of childbearing potential must use contraception one month before screening and continue throughout the study and for the specified duration post-study.

Exclusion:

- Positive ipsilateral supraclavicular or internal mammary lymph nodes.
- Pregnant or lactation.
- Severe non-neoplastic medical comorbidities that preclude radiation treatment (e.g., severe ischemic heart disease, arrhythmia, chronic obstructive pulmonary disease).
- Prior diagnosis of non-breast malignancy within 5 years, except for lobular carcinoma in situ, basal cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the skin, and adenocarcinoma in situ of the lung.
- Synchronous contralateral breast cancer or a prior history of ipsilateral breast cancer (including DCIS).
- Previous RT to thoracic and/or axillary, cervical region.
- Active collagen vascular disease.
- Evidence of distant metastatic disease or T4 disease.

Radiotherapy

General Consideration

Both IMRT and proton therapy are allowed. The main goal overall is to ensure that the prescribed dose covers the PTV in IMRT and CTV in proton therapy while minimizing the radiation dose to OARs. RT should start within 12 weeks after the last date of surgery or 8 weeks after the final dose of planned adjuvant chemotherapy. Planned adjuvant endocrine therapy, immune checkpoint inhibitor, and anti-HER2 therapy are allowed to continue during RT.

Patient Positioning and Immobilization

Patients are positioned supine with arms abducted to at least 90 degrees. The immobilization methods are tailored to each center's standards, prioritizing position stability and repeatability throughout RT to ensure consistent dose delivery.

Thermoplastic masks are recommended for head immobilization.

The computed tomography (CT) based treatment planning with scan thickness of 3–5 mm should start at the level of the cranial base, and extend to at least 4 cm below the ipsilateral or contralateral inframammary fold. Radiopaque markers are used to delineate the surgical scar and breast contour.

When using a proton therapy system with only two-dimensional image guidance, it is recommended to place non-radiopaque metal spheres next to the target volume. These spheres will serve as a reference for position during image registration and should be removed before treatment.

Volumes of Interest

The target volumes include ipsilateral whole breast/chest wall and regional lymphatic regions, including supra/infraclavicular nodes, internal mammary nodes, and any portion of the undissected axilla deemed at risk. An exhaustive atlas detailing these target volumes is provided in **the Appendix File (Table S1, Table S2, Table S3).**

The margins between planning target volume (PTV) and CTV depend on the institutional standards of each study center with a general recommendation of 5-8 mm. OARs including the heart, bilateral lungs, contralateral breast, spinal cord, ipsilateral humeral head, and ipsilateral brachial plexus were contoured based on RTOG guidelines. A "skin ring" should be contoured to evaluate skin doses in proton therapy. For BCS patients, this ring is defined as a 3mm deep tissue layer, while for mastectomy patients, it is a 5mm deep layer from the external body surface.

Prescription and Normal Tissue Constraints

The regimen of 26 Gy in five fractions has been confirmed non-inferior in efficacy and safety to the standard 40 Gy in 15 fractions, as evidenced in the Fast-Forward trial and its nodal sub-study [7, 18]. Thus, for all enrolled patients, the prescribed dose to the ipsilateral chest wall or whole breast and regional lymph region is 2600 cGy in five fractions, once daily over one week. A sequential tumor bed boost of 1040 cGy in two fractions once daily is optional and at the discretion of the radiation oncologist.

The specific dose requirements for the PTV in IMRT, the CTV in the proton

therapy, and dose-volume constraints for OARs are outlined in the **Appendix File (Table S4, Table S5).**

Treatment Planning

Patients undergoing photon therapy are treated with an IMRT technique using 6MV X-rays, as described in the published literature [22]. A 3-5 mm skin bolus is allowed for chest wall irradiation.

For proton therapy, a relative biological effectiveness (RBE) coefficient of 1.1 is applied. Spot-scanning proton therapy is recommended, with passive scattering proton therapy allowed. When using passive scattering, it is best to use at least two fields to reduce skin dose. In spot-scanning proton therapy, range shifters can be used to improve dose coverage for superficial target regions. Adjust proton stopping power ratio (SPR) for non-radiopaque markers to match air's SPR for accurate dose calculations. Calibrate SPR for metallic markers in the tumor bed according to material-specific values. Plan robustness, the capacity of a proton plan to maintain its objectives amidst uncertainties, is essential and should be assessed for each patient's treatment plan. Setup uncertainties are kept within ±3 mm for positioning and ±3.5% for range.

Treatment Verification Schedule and Quality Assurance

For the first five patients at each participating center, a senior radiation oncologist must review and approve the contouring and dose-volume constraints for CTV and OARs. Any deviations from the specified protocol requirements must be documented and should not exceed 10% of enrolled patients.

Before each treatment session, verify patient positioning using an electronic portal imaging device (EPID), cone-beam computed tomography (CBCT), or other available image-guided radiation therapy (IGRT) techniques to ensure any three-dimensional positional discrepancies are < 3mm. If 2D imaging is used in the proton therapy system, non-radiopaque metal spheres are recommended to serve as fiducials for image registration. but these should be removed before treatment.

Criteria for Discontinuing Interventions

Patients can withdraw from the trial at any time without penalty. If they withdraw before starting RT, they will receive standard care according to institutional guidelines. The date of withdrawal will be recorded as the day the study team acknowledges the notification. For patients who experience adverse events, the decision to continue or discontinue RT rests with the principal investigator (PI) or designated medical officer at the participating center, which will be based on an assessment of the event's severity and its potential impact on the patient's health and safety. All adverse events will be documented in the electronic Case Report Form (eCRF) and reported on time. Continued monitoring will be conducted post-withdrawal to ensure safety and proper care. The informed consent form provides details on the criteria for stopping an intervention or withdrawing from the trial.

Endpoints

Primary Endpoint

Acute radiation-induced toxicities: the incidence of Grade ≥ 2 acute toxicities at any time from the start of RT to 6 months after completion.

Secondary Endpoints

- Late radiation-induced toxicities: the incidence of late toxicities at any time from 6 months to 5 years after completion of RT, accessed according to RTOG criteria and CTCAE version 3.0.
- Cosmetic outcomes: for patients undergoing BCS, cosmetic results are evaluated using the the Harvard Breast Cosmesis Scale, ranging from excellent (minimal or no difference compared to the untreated breast), good (slight difference in the size or shape), fair (obvious difference in the size or shape), to poor (marked change in size or shape).
- Local regional recurrence (LRR): the first recurrence in the ipsilateral chest wall, breast, or regional nodes (ipsilateral axillary, supraclavicular, or internal mammary nodes) confirmed by histology or cytology.

- Distant metastasis-free survival (DMFS): time from randomization to the occurrence of distant tumor recurrence, death from any cause, or until the last follow-up.
- Invasive recurrence-free survival (IRFS): time from randomization to the occurrence of invasive tumor recurrence, distant metastases, or death from any cause, or until the last follow-up, including second invasive primaries of the breast.
- Overall survival (OS): time from randomization to death from any cause or until the last follow-up.

Exploratory endpoints of the trial are quality of life using self-administered questionnaires EORTC QLQ-C30 and QLQ-BR23 (Chinese version).

Outcome Measures and Follow-Up

The schedule of enrollment, interventions, and assessments is detailed **in Table 1**. Any radiation-induced toxicities, tumor recurrence events, and deaths must be thoroughly documented in the eCRF. The radiation-induced toxicities are graded using RTOG criteria and CTCAE version 3.0. Survival events will be assessed by physical examination, serum test, ultrasound of the breast, regional nodes, and abdomen every 6 months, breast mammography, and chest CT scan annually after completion of RT. Any additional examinations are at the discretion of clinicians. Lymphedema is defined as a ≥10% increase in arm circumference from baseline or the contralateral arm. Radiation-induced skin injuries and upper limb functional impairments are recorded with photographic and video evidence.

Data Collection and Management

Data collection is facilitated through an eCRF system established by the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. This online system comprises various forms to gather comprehensive data, including baseline information before enrollment, pre-treatment assessments, details of the RT plan, acute toxicities, follow-

up reviews covering survival and toxicity at specified intervals, Quality of Life assessments using standardized questionnaires, and reporting forms for serious adverse events (SAEs). PI, ethical committees, and sponsors have unrestricted access to the database for real-time analysis and monitoring. Each participating center has access to its own data, with the leading investigators being responsible for data quality oversight. Upon trial completion, data quality and integrity are verified by specially trained personnel before the dataset is secured for analysis. All data generated by the study are treated with strict confidentiality. Patient identities will not be disclosed in any public reports or presentations of the study findings. The research center is obligated to retain all pertinent data for a minimum of 5 years post-study completion. Destruction of data is subject to approval by the ethical committee.

Calculation of Samples

The sample size for the trial is calculated using Power Analysis and Sample Size Software (2017) (NCSS, Kaysville, Utah, USA, www.ncss.com/software/pass).

Sample for the ARROW trial

The probability of a Type I error is 0.05, and the test power is 80%. The acceptable threshold (δ) is 10%. Previous studies have shown that the incidence of acute radiation-induced toxicity in patients receiving conventional fractionated RNI is 45% [22, 24, 25]. Assuming the incidence of grade 2 or higher acute radiation-induced toxicity is less than 55%, and adopting a non-inferiority test, then a total of 177 patients need to be enrolled. In consideration of an expected dropout rate of 10%, the sample size for this study is determined to be 197 cases.

Statistical Analysis

All efficacy and safety analyses will be based on the intention-to-treat principle, and a per-protocol analysis will be performed for the primary endpoint. Acute and late toxicities will be summarized by frequency and severity based on their association with the protocol treatment. Cumulative proportions of time to survival endpoints such as

DMFS, IRFS, and OS will be described using the Kaplan-Meier method. Severe radiation-related toxicity events will be listed individually. The t-test will be used for the comparison of continuous variables. Statistical analysis will be performed using SPSS software version 21.0 (IBM Corporation, Armonk, NY, USA).

Monitoring

The trial is overseen by a Trial Steering Committee (TSC), with leading investigators from all participating centers. The TSC ensures that the trial follows the protocol and ethical guidelines. Study coordination, monitoring, data acquisition, management, and statistical analysis are conducted by a team of statisticians at Ruijin Hospital affiliated with Shanghai Jiao Tong University School of Medicine. This team ensures the integrity and quality of the data collected throughout the trial. An Independent Data Safety and Monitoring Committee (DSMC) is established to oversee the safety and data quality of the trial. The DSMC monitors the progress of the trial, reviews safety data, and assesses the quality of the data. Using the available data, the DSMC makes recommendations to the TSC regarding the continuation of the trial.

Adverse Event Management

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease that occurs during the trial, regardless of whether it is related to RT. Serious adverse events (SAEs) must be reported to the ethical committee within 24 hours of the PI's awareness. If an SAE occurs, all anti-tumor treatments must be halted immediately, and the patient must be monitored until the event is resolved or stabilized, even if it leads to the patient's withdrawal from the study.

The details of SAEs, including the time of onset, severity, expectedness, duration, measures taken, and outcomes, must be meticulously recorded in the eCRF. Reporting of all AEs to the ethical committee and the PI is mandatory at regular intervals, typically every 6 to 12 months.

Ethics and Dissemination

The clinical trial has been approved by the Ethical Committee of Ruijin Hospital affiliated with Shanghai Jiao Tong University School of Medicine, as well as by the ethical committees of all participating centers. This demonstrates our commitment to conducting research that follows the highest ethical standards. Any changes to the protocol will be carefully documented and submitted for ethical committee review and approval before being implemented. This strict oversight ensures that all trial modifications are in the best interest of the participants and the scientific integrity of the study. The study follows the Declaration of Helsinki and adheres to Good Clinical Practice (GCP) guidelines to ensure the protection of human rights, safety, and well-being of all trial participants.

Participants will provide informed consent before enrolling to ensure full awareness of the study's objectives, procedures, benefits, and risks. Upon completion of the research, findings will be prepared for submission to peer-reviewed journals. Authorship will be reserved for individuals who have made significant contributions to the study's design, conduct, and analysis. The final clinical study reports and their summaries will be disseminated to the local ethical committees, institutes, and sponsors involved in the protocol, ensuring transparency and accountability in the research process.

Patient and Public Involvement

In the design, execution, reporting, and dissemination of our research, we have not engaged patients or members of the public. The research team developed and conducted the study without direct input from these groups.

Discussion

Short-course RT offers several advantages, including reduced use of scarce resources, realized work time and cost savings, increased throughput, reduced waiting times, and decreased non-medical expenses for patients [26]. Following the publication of the 5-

year outcomes from the Fast-Forward trial, there has been a surge of interest in one-week regimens, prompting the initiation of multiple studies (Table 2). In these ongoing trials, there are significant variations in the specifications for tumor bed boost and IMNI. Our trial innovates by extending the application of ultra-hypofractionated regimens to sequential tumor bed boosts and IMNI. The ultra-hypofractionated tumor bed boost limits the RT course to a maximum of 1.5 weeks, with a single fractional dose consistent with WBI and RNI, offering a more convenient clinical strategy. The trial also allows the enrollment of patients who have undergone breast reconstruction, received neoadjuvant treatment, and those with positive sentinel lymph nodes (SLN) but no axillary lymph node dissection (ALND). This provides a better representation of the real-world patient population.

The main concern regarding IMNI is the increased risk of cardiac and pulmonary toxicity, especially for left-sided patients. Due to reduced cardiac and lung doses with the use of advanced RT techniques, the overall benefits of IMNI have been demonstrated in multiple prospective clinical trials [2, 4-6, 20, 21]. The MA20 study showed a notable improvement in disease-free survival (DFS) for the RNI group, including IMNI, compared to the group without RNI [2]. Echoing these findings, the EORTC 22922/10925 study revealed a significant reduction in breast cancer mortality and any recurrence among patients who received RNI, including IMNI [21, 27]. Furthermore, the DBCG-IMN study substantiated the positive impact of IMNI on reducing the risk of distant recurrence and breast cancer mortality, thereby enhancing long-term survival [5, 28]. Of note, no excess cardiac mortality with IMNI was observed in these trials [2, 5, 21, 27-29]. In light of these findings, the ARROW trial mandates IMNI for all participants, with the expectation that it will yield data on the safety of the ultra-hypofractionated regimen for RNI, including IMNI. Considering the concerns regarding cardiac and pulmonary toxicity, our study protocol included follow-up assessments of cardiac function using electrocardiography and echocardiography, as well as monitoring for radiation pneumonitis using chest CT scans. This can provide more comprehensive safety data for the one-week regimen of IMNI.

In addition, the ARROW trial allows for the inclusion of patients with positive SLNs but no ALND. The pivotal studies such as Z0011, AMAROS, IBCSG 23–01, and SANOMAC have demonstrated that omission of ALND is non-inferior to ALND in terms of oncologic outcomes for patients with positive SLNs [30-33]. Driven by the findings from these trials, an increasing number of patients with positive SLNs are being spared from ALND in clinical practice. Axillary RT, as demonstrated by the AMAROS trial, was non-inferior to ALND in terms of overall survival (OS), DFS, and locoregional control. Furthermore, axillary RT showed a reduction in the incidence of lymphedema compared to ALND [30]. In a prospective screening trial, Taghian et al [34] found that the ALND-only group had a significantly higher risk of breast cancer-related lymphedema compared to the group receiving SLN biopsy plus RNI (24.9% vs. 10.7%, p = 0.02). However, the impact of ultra-hypofractionated RNI, including axillary RT, on oncologic outcomes and radiation-induced toxicities such as lymphedema in these patients remains to be determined. The ARROW trial aims to provide preliminary data on the feasibility of ultra-hypofractionated RNI in patients with SLNs but no ALND.

Tumor bed boost has been shown to reduce the local recurrence in high-risk patients undergoing BCS [35]. However, determining the optimal fractionation scheme for tumor bed boost in the era of short regimens remains a topic of debate. The Fast-Forward trial adhered to a conventional fractionation approach, prescribing tumor bed boosts of 10 Gy or 16 Gy in 2 Gy fractions sequential to WBI [19]. Not all ongoing one-week regimen trials have disclosed detailed protocols for tumor bed boost. There are also variations in the dose fraction for the tumor bed boost. For instance, the HYPORT trial (NCT03788213) of WBI or chest wall irradiation with or without RNI permits both a simultaneous integrated boost (SIB) of 32 Gy in 5 fractions and a sequential boost of 12 Gy in 4 fractions. Another trial of WBI (NCT05586256) offers an SIB of 30 Gy in 5 fractions or a sequential boost of 7.6 Gy in 2 fractions. Our trial diverges from other single-week regimen trials by administering a sequential tumor bed boost of 10.4 Gy in 2 fractions, aligning with the single fractional dose used for WBI

and RNI to make it convenient for clinical practice. We expect to contribute evidence on the safety of a sequential ultra-hypofractionated tumor bed boost.

One of the critical challenges in implementing ultra-hypofractionated regimens is the high demand for precision in both patient positioning and dose delivery. To address this, we employed daily CBCT imaging, ensuring positional errors in three dimensions do not exceed 3mm. Additionally, our trial utilizes IMRT and proton therapy to minimize the dose to OARs as much as possible, particularly for the left-sided IMNI. Incorporating daily imaging-guided RT and state-of-the-art RT techniques has the potential to enhance the safety of the ultra-hypofractionated regimen. The technical details in our protocol could provide a framework for the broader clinical adoption of ultra-hypofractionated regimens in the future.

The ARROW trial holds significant importance in exploring the safety and efficacy of ultra-hypofractionated regimens for RNI including IMN and sequential tumor bed boost in early breast cancer patients. The results of our trial are expected to pave the way for the broader adoption of ultra-hypofractionated regimens among postoperative RT breast cancer patients. Furthermore, the IMRT and proton therapy used in our trial can provide more favorable dose distributions for the target volume and OARs, while offering data for implementing an ultra-hypofractionated regimen with these state-of-the-art RT techniques.

Declarations

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Authors' contributions

LC and JC design the original protocol for the study. JX and SZ contributed to study management and drafted the manuscript. WQ performed the sample size calculation

and data analysis. All authors participated in enrollment and follow-up of patients. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of Shanghai Jiao Tong University School of Medicine affiliated Ruijin Hospital (IEC approval number for ARROW 1.3: 2020-167-4, Date:2024-09-13). Written informed consent is obtained from all participants before study participation. See **Additional file 1** for the SPIRIT checklist of the study protocol.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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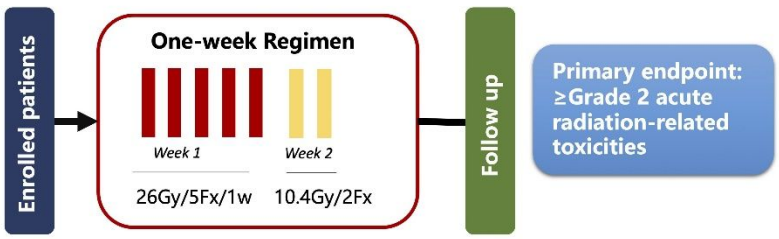
Figure legend

Figure 1 Study design



Abbreviations: Fx=fractions,

Table 1 Schedule of enrollment, interventions, and assessments

	STUDY PERIOD										
	Pre-radiotherapy	Interventions: Radiotherapy		Post-radiotherapy							
TIMEPOINTs	**baseline**	**1w**	**2w**	**4w**	**6m**	**12m**	**18m**	**2y**	**3y**	**4y**	**5y**
ENROLLMENT:											
Eligibility screening	X										
Informed consent	X										
INTERVENTIONS:											
Ultra Hypofractioned regimen		X	X								
ASSESSMENTS:											
History and Physical Examination	X	X	X	X	X	X	X	X	X		X
Chest CT scan	X[a]					X		X	X		X
Mammography						X		X	X		X
Ultrasound for Breast and regional nodes	X				X	X	X	X	X		X
ECG	X				X	X	X	X	X		X
Echocardiography	X				X	X	X	X	X		X
Cosmetic outcomes for BCS	X			X	X	X	X	X	X		X
Quality of life	X			X	X	X	X	X	X		X

[a] Simulation CT is acceptable

Abbreviations: CT = Computed Tomography; ECG = Electrocardiogram; BCS = Breast-Conserving Surgery; w=week, m=month; y=years

Table 2 The ongoing trials on the one-week regimen for WBI alone and for RNI in early breast cancer

NCT Number	Country	Age (years)	Start year	Randomized	Enrolled patients	Reconstruction	Tumor bed Boost	IMNI	Study group	Control group	Sample size	Primary Endpoint	Status
WBI alone													
NCT05586256	Italy	18-99	2021	No	Indicated for WBI	N/A	Optional, SIB of 30Gy/5Fx or sequential 7.6Gy/ 2Fx	N/A	26Gy/5Fx/1w	N/A	300	Acute and chronic toxicity	Recruiting
NCT05318274	Mexico	≥18	2021	Yes	BCS, pTis-T2, N0	N/A	Study group: No boost; Control group: SIB of 48Gy/16Fx in high risk patients	N/A	26Gy/5Fx/1w	42.5Gy/16Fx/1	72	Local control	Recruiting
NCT04669873	Brazil	50-90	2021	Yes	BCS, unifocal disease, T＜3cm，pN0, negative LVSI, Grade 1-2,	N/A	No	N/A	Group1: 26Gy/5Fx/1w for WBI Group2: 26Gy/5F	40Gy/15Fx/3w for WBI	36	Local recurrence	Recruiting

					margin＞2mm				x/1w for PBI				
NCT05417516	Canada	≥50	2023	Yes	BSC, negative margin, N0	N/A	No	N/A	26Gy/5Fx/1w for PBI	26Gy/5Fx/1w for WBI	910	Local recurrence	Recruiting
RNI													
NCT03788213	India	≥18	2019	Yes	BCS, or after NAC, or mastectomy with pT3/T4 or pN2 or pT0-2pN0-1 with a Cambridge Score of 3 or more	Yes	Study group:SIB of 32Gy/5Fx, or sequential 12Gy/4Fx; Control group: SIB of 48Gy/15Fx, or sequential 12Gy/4Fx	Based on institutional policy	26Gy/5Fx/1w for WBI/Chest wall, and RNI in N+ or after NAC	40Gy/15Fx/3w for WBI/chest wall and RNI in N+ or after NAC	2100	Locoregional recurrence rate	Recruiting
NCT04648904	United States	≥30	2020	No	mastectomy with reconstruction; pathologic T0N1a-2a, T1N1a-2a,	Yes	Optional chest wall boost of 5.2 Gy for 1-2 fractions or 2.5 Gy for 1-4 fractions	Not mentioned	26Gy/5Fx/1w	N/A	72	Local and regional recurrences	Recruiting

					T2N1a-2a, T3N0-2a, all M0								
NCT04443413	United States	≥18	2020	Yes	BCS or mastectomy; clinical or pathologic T1-T4c, N0-3, M0; indicated for RNI	Not mentioned	Optional Study group: SIB of 5-fraction; Control group: 4-fraction boost of x-ray therapy	Not mentioned	proton therapy over 5 fractions	x-ray therapy over 5 fractions	146	Complication rate	Recruiting
NCT04228991	Canada	≥18	2021	Yes	BCS or mastectomy; pT3N0, pT1-3N1-2; Or NAC with cT3N0, cT1-3N1-2 and ypT0-3N0-2	No	Not mentioned	Not mentioned	26Gy/5Fx/1w	40Gy/15Fx/3w	588	Lymphedema	Recruiting
NCT04472845	India	≥18	2021	Yes	BCS or mastectomy; pT3-4pN2-3 M0; NAC with clinical	Tissue expanders with distant metal ports	Study group: SIB of 34Gy/5Fx or sequential 8Gy/2Fx/2d; Control	for patients with T3-4 central and	26Gy/5Fx/1w	34Gy/10Fx/2w	1018	Locoregional control	Recruiting

					stage III or ypN+	are allowed	group: SIB of 42Gy/10fx/2w or sequential 8Gy/2Fx/2d	inner quadrant lesions and patients with N2					
NCT05150535	Egypt	≥45	2021	Yes	BCS or mastectomy; TxN1-3M0, T0-2N2-3M0, T3-4N0-3M0; Or LABC with NAC	Not mentioned	Study group: SIB of 32Gy/5Fx or sequential 12Gy/ 4Fx; Control group: SIB of 48Gy/15Fx, or sequential 12Gy/4Fx	For patients with N2-3	26Gy/5Fx/1w for WBI/Chest wall, and RNI in N+ or after NAC	40Gy/15Fx/3w for WBI/Chest wall and RNI in N+ after NAC	100	Acute and chronic grade 2 toxicity or higher	Unknown
NCT05665920	Brazil	≥18	2022	Yes	BCS; pT1-3 and pN1-3a; with indication of RNI	N/A	Not mentioned	No	26Gy/5Fx/1w	40Gy/15Fx/3w	36	Locoregional recurrence	Recruiting

Abbreviations: WBI = Whole Breast Irradiation; RNI = Regional Nodal Irradiation; IMNI = Internal Mammary Nodal Irradiation; N/A = Not Applicable; SIB = Simultaneous Integrated Boost; w = week; d = days; BCS = Breast-Conserving Surgery; LVSI = Lymphovascular Space Invasion; PBI = Partial Breast Irradiation: NAC = Neoadjuvant Chemotherapy; LABC = Locally Advanced Breast Cancer.

the study design

1058x253mm (96 x 96 DPI)

Additional File

Page2:

Table S1 Anatomical boundaries of Chest wall/whole breast CTV

Page3-4:

Table S2 Anatomical boundaries of CTV for regional nodes

Page5:

Table S3 Tumor bed boost contours

Page6-7:

Table S4 Dosimetric coverage for target volume

Page8-9:

Table S5 Dose constraints for OARs

Table S1. Anatomical boundaries of chest wall and whole breast CTV

	Chest wall	Whole breast
Cranial	Guided by palpable /visible signs; if appropriate guided by the contralateral breast; maximally up to the inferior edge of the sternoclavicular joint	Upper border of palpable /visible breast tissue; maximally up to the inferior edge of the sternoclavicular joint
Caudal	Guided by palpable/visible signs; if appropriate guide by the contralateral breast	Clinical reference; last caudal CT slice with visible breast
Anterior	Skin	5mm under skin surface
Posterior	Include pectoralis muscles, chest wall muscles, excluding ribs	Exclude pectoralis muscles, chest wall muscles, ribs
Lateral	Guided by palpable/visible signs; if appropriate guide by the contralateral breast. Usually anterior to the mid-axillary line, excludes lattices dorsi muscle	Lateral breast fold, anterior to the lateral thoracic artery
Medial	Lateral to the medial perforating thoracic internal vessels; maximally to the edge of the sternum	Lateral to the medial perforating thoracic internal vessels; maximally to the edge of the sternum

Notes: For patients with stage III according to AJCC 8th edition, the posterior of the whole breast can extend to the rib interface.

Table S2. Anatomical boundaries of regional nodal CTV

	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Medial Supra-clavicular	Caudal to the cricoid cartilage	Junction of brachioceph-axillary veins / Caudal edge clavicle head	Posterior edge of sternocleidomastoid muscle	Posterior surface of internal carotid artery or anterior surface of scalene muscles	Medial border of clavicle head 5 mm below the skin surface	Medial border of internal carotid vessels
Lateral Supra-clavicular*	Caudal to the cricoid cartilage	Junction of Brachioceph. - axillary veins. /Caudal edge clavicle head	Posterior surface of internal carotid artery or anterior surface of scalene muscles	At the trapezius	Medial border of clavicle head 5mm below the skin surface	At the longus coli
Internal mammary	Junction of Brachioceph-axillary veins.	Cranial side of the 4rd rib (in selected cases 5th rib)	Ventral limit of the vascular area	Pleura	7mm from internal mammary vessels	7mm from internal mammary vessels
Axilla-level I	Below the humeral head	At the point where the pectoralis major inserts on the ribs (around 4th to 5th rib)	At posterior pectoralis major & minor muscles	An imaginary line anterior to the surface of latissimus dorsi muscle, subscapularis muscle and teres major muscle	Cranially up to an imaginary line between the major pectoral and deltoid muscles and further caudal up to a line between the major pectoral and latissimus dorsi muscles	Lateral border of pectoralis minor musle

Axilla-level II	Insertion point of pectoralis minor muscle	The caudal border of the pectoralis minor muscle	Pectoralis minor muscle	Anterior border of ribs and serratus anterior	Lateral edge of pectoralis minor muscle	Medial edge of pectoralis minor muscle
Axilla-level III	Pectoralis minor muscle insert on Coracoid	Axillary vessels cross medial edge of pectoralis minor muscle	Posterior surface of pectoralis major muscle	Anterior border of ribs or posterior border of subclavian or axillary vessels	Medial border of pectoralis minor muscle	Lateral border of clavicle, ribs, junction of brachioceph-axillary veins.

Notes:

1) The regional nodal CTV target volume should include the medial supra-clavicular, axilla-level III, undissected axilla-level II, and internal mammary lymph nodes.
2) The inclusion of axilla-level I and II in the regional nodal CTV is at the discretion of radiation oncologists based on the clinical treatment indications. The rotter's nodes are included in the CTV target volume of axilla-level II.
3) For N2, N3, or high-risk N1 patients, it is recommended to include the lateral supra-clavicular nodes in the regional nodal CTV.
4) When the tumor is in the inner lower quadrant, the caudal border of internal mammary nodes is recommended to extend to the cranial side of the 5th rib.

Table S3. Tumor bed GTV and CTV contours

GTV	Includes seroma and surgical clips
CTV	GTV with a margin of 1 cm in all directions and without exceeding CTV of the whole breast

Abbreviations: GTV= CTV=clinical target volume,

Table S4. Dosimetric coverage for target volume

Target volume		Requirements
PTV of chest wall/whole breast and RNI	Per Protocol	D95%>42.5Gy
	Acceptable variation	D90%>42.5Gy
	Per Protocol	V28Gy<100%
	Acceptable variation	V29Gy<100%
	Per Protocol	V25Gy>99%
	Acceptable variation	V24Gy>99%
CI for PTV of chest wall/whole breast and RNI	Per Protocol	≥0.95 and ≤2
	Acceptable variation	≥0.85 and ≤2.5
Tumor bed PTV	Per Protocol	D95%>36.4Gy
	Acceptable variation	D90%>36.4Gy
	Per Protocol	V39Gy<5%
	Acceptable variation	V40Gy <5%
	Per Protocol	V35Gy >99%

	Acceptable variation	V34Gy≥39%
CI for Tumor bed PTV	Per Protocol	≥0.95 ≥2.5
	Acceptable variation	≥0.9 ≥3

Notes:

1) When evaluating the treatment plan of chest wall/whole breast with RNI, tumor bed boost doses should not be considered.
2) CI=Conformity index, the volume covered by 95% of the prescription dose / PTV volume
3) For evaluation of IMRT plan: a) The whole breast CTV is expanded by 5-8mm in three dimensions to form the PTV. The PTV is limited to 5mm below the skin and the surface of the pectoral muscle or chest wall to form the whole breast PTV_eval for IMRT plan evaluation; 2) The chest wall and regional nodal CTV is expanded by 5-8mm in three dimensions to form an integrated PTV; Limit the PTV to the skin as the anterior boundary and the chest pleura as the posterior boundary to form the PTV_eval for plan evaluation.
4) For evaluation of proton plan: a) the dosimetric coverage of the CTV is evaluated; b) The chest wall CTV is recommended to retract 5mm from skin; c) If the chest wall is very thin, 3mm can be considered.

Table S5. DVH constraints for OARs

OARs	The ARROW trial			The SHIFT trial		
	Dosimetric parameter	Per protocol	Acceptable variation	Dosimetric parameter	Per protocol	Acceptable variation
Heart for left-sided breast cancer	Mean	<3Gy	<3.5Gy	Mean	<2Gy	<2.5Gy
	V15Gy	<10%	<15%	V7Gy	<4%	<5%
	V4Gy	<20%	<25%	V5Gy	<10%	<12%
	N/A	N/A	N/A	V1.5Gy	<27%	<30%
Heart for right-sided breast cancer	Mean	<1Gy	<1.5Gy	Mean	<1Gy	<1.2Gy
	V2Gy	<15%	<20%	V1.5Gy	<10%	<15%
Ipsilateral Lung	Mean	<7.5Gy	<8Gy	Mean	<15Gy	<16Gy
	V4Gy	<45%	<50%	V10Gy	<12%	<15%
	V10Gy	<30%	<35%	V8Gy	<15%	<18%
	V15Gy	<20%	<23%	N/A	N/A	N/A
Contralateral lung	Mean	<1Gy	<1.5Gy	Mean	<1Gy	<1.2Gy
	V2Gy	<10%	<15%	N/A	N/A	N/A
Spinal cord	Max	<20Gy	N/A	N/A	N/A	N/A

Ipsilateral Humeral head	Mean	<10Gy	<11Gy	N/A	N/A	N/A
Contralateral breast	Mean	<3.5Gy	<5Gy	Mean	<2Gy	<3Gy
Brachial plexus	D0.1cc	<27Gy	<28Gy	N/A	N/A	N/A
the skin ring	D1cc	<27.3Gy	N/A	<27.3Gy	N/A	N/A

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Page	Section/item	Item No	Description
	Administrative information		
1	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
3	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
		2b	All items from the World Health Organization Trial Registration Data Set
19	Protocol version	3	Date and version identifier
19	Funding	4	Sources and types of financial, material, and other support
1,18	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
1		5b	Name and contact information for the trial sponsor
18		5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
14		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
	Introduction		

4	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
Not applicable		6b	Explanation for choice of comparators
5	Objectives	7	Specific objectives or hypotheses
5	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
	Methods: Participants, interventions, and outcomes		
5	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
6-8	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
5,8-10	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
10		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
6,12		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
8		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial

11-12	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
12,24	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
6,12	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
	Methods: Assignment of interventions (for controlled trials)		
	Allocation:		
Not applicable	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Not applicable	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Not applicable	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Not applicable	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
Not applicable		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
12	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
6,12		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
12	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
13-14	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

13-14		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
13-14		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
14	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
Not applicable		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
14	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
14	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
15,19	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
15	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

6,19	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
Not applicable		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
12	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
19	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
12-14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
14-15	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
15	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
15		31b	Authorship eligibility guidelines and any intended use of professional writers
Not applicable		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
	Appendices		
19	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates

Not applicable	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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One-Week Regimen for Post-Operative Regional Irradiation in Breast Cancer: The ARROW Trial Protocol

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One-Week Regimen for Post-Operative Regional Irradiation in Breast Cancer: The ARROW Trial Protocol

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Abstract

Introduction: Shortening the duration of postoperative radiotherapy (RT) for breast cancer while maintaining efficacy and safety has become a significant trend. The three-week regimen of 40–42.5 Gy in 15–16 fractions is now a preferred option in clinical practice. Following the publication of the 5-year outcomes from the Fast-Forward trial, interest in one-week regimens has surged, prompting the initiation of multiple studies. However, trials exploring the one-week regimen for regional nodal irradiation (RNI), especially involving internal mammary nodes (IMN), remain scarce. Additionally, the optimal fractionation scheme for tumor bed boost in the era of ultra-hypofractionated regimens is still debated. To address these gaps, we initiated the ARROW trial to evaluate the feasibility of a one-week regimen for RNI of 26 Gy in five fractions, with optional sequential tumor bed boost of 10.4 Gy in two fractions. The findings from our trial are expected to extend the application of ultra-hypofractionated regimens to include sequential tumor bed boosts and RNI, pioneering its use in IMN irradiation.

Methods and Analysis: The ARROW trial is an open-label, single-arm, multi-center Phase II trial, encompassing four teaching hospitals in China. Enrolled patients will receive a total of 26 Gy in five fractions to ipsilateral whole breast/chest wall and regional regions, including supra/infraclavicular nodes, IMN, and any portion of the undissected axilla deemed at risk. A sequential tumor bed boost of 10.4 Gy in 2 fractions is delivered in patient at high risk for recurrence, which is at the discretion of the radiation oncologist. The sample size for the ARROW trial was 197 patients. Both Intensity-Modulated Radiation Therapy (IMRT) and proton therapy are permitted. The primary endpoint is acute radiation-induced toxicity, graded according to RTOG criteria and CTCAE version 3.0. Secondary endpoints include cosmetic outcomes for breast conserving surgery, late radiation-induced toxicity, local-regional recurrence, distant metastasis, invasive tumor-free survival, overall survival, and quality of life assessment.

Ethics and dissemination: The trial has been approved by the Ethical Committee of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, as well

as approvals from the ethical committees of each participating center have also been obtained. Research findings will be submitted for publication in peer-reviewed journals.

Trial registration:

ARROW trial: NCT04509648

Strengths and limitations of this study

- The ARROW trial evaluates the feasibility of a one-week regimen for RNI of 26 Gy in five fractions in China.
- A sequential tumor bed boost of 10.4 Gy in 2 fractions is used in the trial.
- Both Intensity-Modulated Radiation Therapy and proton therapy are permitted.
- One of the limitations is that this study does not stratify according to clinicopathological, subtype, or gene information.
- Another limitation is that this trial is a single-arm phase II study; however, it could provide the safety profile of the ultra-hypofractionated regimen in tumor bed boost and IMNI, serving as a foundation for initiating a subsequent phase III randomized controlled trial of one-week regimen.

Background

Breast cancer is the most prevalent malignant tumor among women [1]. Postoperative radiotherapy (RT) can significantly reduce recurrence risk and improve survival for patients undergoing breast-conserving surgery (BCS) or those at high-risk post-mastectomy [2-6]. However, the traditional 5-7 weeks RT regimen may reduce patient compliance and strain limited RT resources. The UK START trials identified an α/β value of approximately 3.5 Gy for breast cancer tissue, indicating that hypofractionated (HF) RT, with higher single-fraction doses, is more suitable for breast cancer [7].

In recent years, evidence from randomized trials and real-world studies has established the three-week regimen of 40-42.5 Gy in 15-16 fractions as the preferred option for whole breast irradiation (WBI) [7-13]. This practice has gradually expanded to include regional nodal irradiation (RNI) [14-17]. In a randomized trial with a median follow-up of 58.5 months, Wang et al [15] demonstrated that HF-RNI of 43·5 Gy with 2.67 Gy per fraction was non-inferior to the five-week regimen of 50 Gy with 2 Gy per fraction for locoregional control and adverse effects.

The Fast-Forward trial marked a pivotal advancement by condensing the RT regimen to one week for WBI using ultra-hypofractionation [18]. With a median follow-up of 71.5 months, this trial demonstrated that a one-week regimen of 26 Gy in five fractions was non-inferior in local control and normal tissue effects compared to the standard three-week regimen of 40 Gy in 15 fractions. However, this trial gave the tumor bed boost using conventional fraction, extending the overall RT duration to 2 or 2.5 weeks. The feasibility of ultra-hypofractionation in the tumor bed boost irradiation remains unknown. The Nodal Sub-Study of the Fast-Forward trial further explored the non-inferiority of the one-week regimen of RNI in patient-reported arm/hand swelling [19]. This study excluded patients with an indication of internal mammary nodal irradiation (IMNI) due to the perceived uncertainty of its value at the time of protocol design. With advancements in RT technology, there has been a significant reduction in heart and lung doses associated with IMNI, leading to increasing recognition of its benefits in recent years [2, 4-6, 20, 21]. However, limited data is available on the use of a one-week regimen in IMNI.

To fill in these gaps, we initiated the ARROW trial to evaluate the feasibility of a one-week regimen for RNI of 26 Gy in five fractions for early breast cancer, with optional sequential tumor bed boost of 10.4 Gy in two fractions. The results from our trial are expected to confirm the feasibility of a one-week regimen and extend the use of ultra-hypofractionated regimens to include sequential tumor bed boosts and RNI, pioneering its application in IMNI.

Methods

Study Design

The ARROW trial is an open-label, single-arm, multi-center Phase II trial being conducted at four teaching hospitals in China. The primary objective is to assess the feasibility of a one-week regimen of 26 Gy in five fractions for early breast cancer patients. Both Intensity-Modulated Radiation Therapy (IMRT) and proton therapy are permitted. The primary endpoint is the incidence of Grade ≥ 2 acute radiation-induced toxicities at any time from the start of RT to 6 months after completion. Secondary endpoints include cosmetic outcomes for patients with BCS, late radiation-induced toxicity, local-regional recurrence, distant metastasis, invasive tumor-free survival, overall survival, and quality of life. The radiation-induced toxicity was graded using RTOG criteria and CTCAE version 3.0.

In the ARROW trial, participants receive 26 Gy in five fractions for the ipsilateral whole breast or chest wall (detailed in Table S1) and regional lymphatic regions, including supraclavicular and internal mammary nodes, and any portion of the undissected axilla deemed at risk (detailed in Table S2). A sequential tumor bed boost of 10.4 Gy in two fractions is delivered in patient at high risk for recurrence, which is at the discretion of the radiation oncologist. **Figure 1** illustrates the study design of the trial. The ARROW trial (NCT04509648) is registered on ClinicalTrials.gov.

Participants and Recruitment

The clinical team will identify and approach eligible patients during their initial visit to the Department of Radiation Oncology, offering the opportunity for potential study

participation. They are provided with a comprehensive overview of the study's objectives, procedures, benefits, and risks to thoroughly understand their involvement. Those who express interest, meet the inclusion criteria, and fully comprehend the study's implications will be invited to provide written informed consent. Following voluntary consent, participants will be officially enrolled in the study.

The first patient of the ARROW trial was enrolled on 21 January 2021 and is expected to complete enrollment by December 2025.

Inclusion and Exclusion Criteria

Inclusion:

- Aged >18 years old.
- Pathologically invasive breast cancer.
- Undergoing BCS or mastectomy with reconstruction allowed, along with axillary lymph node dissection or sentinel lymph node biopsy.
- Axillary lymph node metastasis confirmed histologically (involving one or more nodes), or node-negative axilla with an indication for RNI as determined by the radiation oncologist.
- Karnofsky Performance Status scoring ≥80, and anticipative overall survival >5 years.
- Surgery wound healed without infection.
- Negative pathologically surgical margin.
- Estrogen-receptor, Progesterone-receptor, HER-2, and Ki67 index assessment on the primary breast tumor or axillary nodes is feasible.
- Women of child-bearing potential must agree to use adequate contraception for up to 1 month before study treatment and the duration of study participation.

- Ability to understand and willingness to participate the research and sign the consent forms.

Exclusion:

- Pathologically positive ipsilateral supraclavicular lymph node.
- Pathologically or radiologically confirmed involvement of ipsilateral internal mammary lymph nodes.
- Pregnant or lactating women.
- Severe non-neoplastic medical comorbidities that preclude radiation treatment (e.g., severe ischemic heart disease, arrhythmia, chronic obstructive pulmonary disease).
- History of non-breast malignancy within 5 years with the exception of lobular carcinoma in situ, basal cell carcinoma of the skin, carcinoma in situ of skin, adenocarcinoma in situ of the lung and carcinoma in situ of the cervix.
- Simultaneous contralateral breast cancer or a prior history of ipsilateral breast cancer (including DCIS).
- Previous RT to the neck, chest and/or ipsilateral axillary region.
- Active collagen vascular disease.
- Definitive pathological or radiologic evidence of distant metastatic disease.
- Primary T4 tumor.

Radiotherapy

General Consideration

Both IMRT and proton therapy are allowed. The main goal is to ensure that the prescribed dose covers the PTV in IMRT and CTV in proton therapy while minimizing

the radiation dose to organs-at-risk (OARs). Proton therapy is prioritized for left-sided IMNI, patients at high risk of radiation-induced toxicities or cases where heart or lung dose constraints cannot be achieved with IMRT. In centers without proton facilities, IMRT is used as the standard approach. RT should start within 12 weeks after the last date of surgery or 8 weeks after the final dose of planned adjuvant chemotherapy. Planned adjuvant endocrine therapy, immune checkpoint inhibitor, and anti-HER2 therapy are allowed to continue during RT.

Patient Positioning and Immobilization

Patients are positioned supine with arms abducted to at least 90 degrees. The immobilization methods are tailored to each center's standards, prioritizing position stability and repeatability throughout RT to ensure consistent dose delivery. Thermoplastic masks are recommended for head immobilization.

The computed tomography (CT) based treatment planning with scan thickness of 3–5 mm should start at the level of the cranial base, and extend to at least 4 cm below the ipsilateral or contralateral inframammary fold. Radiopaque markers are used to delineate the surgical scar and breast contour.

When using a proton therapy system with only two-dimensional image guidance, it is recommended to place non-radiopaque metal spheres next to the target volume. These spheres will serve as a reference for position during image registration and should be removed before treatment.

Volumes of Interest

The target volumes include ipsilateral whole breast or chest wall and regional lymphatic regions, including supra/infraclavicular nodes, internal mammary nodes, and any portion of the undissected axilla deemed at risk. An exhaustive atlas detailing these target volumes is provided in **the Appendix File (Table S1, Table S2, Table S3).**

The margins between planning target volume (PTV) and CTV depend on the institutional standards of each study center with a general recommendation of 5-8 mm. OARs including the heart, bilateral lungs, contralateral breast, spinal cord, ipsilateral humeral head, and ipsilateral brachial plexus were contoured based on RTOG guidelines. A "skin ring" should be contoured to evaluate skin doses in proton therapy.

For BCS patients, this ring is defined as a 3mm deep tissue layer, while for mastectomy patients, it is a 5mm deep layer from the external body surface.

Prescription and Normal Tissue Constraints

The regimen of 26 Gy in five fractions has been confirmed non-inferior in efficacy and safety to the standard 40 Gy in 15 fractions, as evidenced in the Fast-Forward trial and its nodal sub-study [7, 18]. Thus, for all enrolled patients, the prescribed dose to the ipsilateral whole breast or chest wall and regional lymph region is 2600 cGy in five fractions, once daily over one week. A sequential tumor bed boost of 1040 cGy in two fractions once daily is delivered in patient at high risk for recurrence, which is at the discretion of the radiation oncologist.

The specific dose requirements for the PTV in IMRT, the CTV in the proton therapy, and dose-volume constraints for OARs are outlined in the **Appendix File (Table S4, Table S5).**

Treatment Planning

Patients undergoing photon therapy are treated with an IMRT technique using 6MV X-rays, as described in the published literature [22]. A 3-5 mm skin bolus is allowed for chest wall irradiation.

For proton therapy, a relative biological effectiveness (RBE) coefficient of 1.1 is applied. Pencil beam scanning (PBS) proton therapy is recommended, with passive scattering proton therapy allowed. When using passive scattering, it is best to use at least two fields to reduce skin dose. In PBS proton therapy, range shifters can be used to improve dose coverage for superficial target regions. Radiopaque markers on the patient's surface, including the ball bearing for isocenter localization and the wire marking the scar, were contoured and assigned a stopping power ratio (SPR) matching that of air to ensure accurate dose calculations. For the surgical clip within the tumor bed, the SPR was set according to material-specific values from the product brochure. Plan robustness, the capacity of a proton plan to maintain its objectives amidst uncertainties, is essential and should be assessed for each patient's treatment plan. Setup uncertainties are kept within ±3 mm for positioning and ±3.5% for range.

Treatment Verification Schedule and Quality Assurance

For the first five patients at each participating center, a senior radiation oncologist must review and approve the contouring and dose-volume constraints for CTV and OARs. Any deviations from the specified protocol requirements must be documented and should not exceed 10% of enrolled patients.

Before each treatment session, verify patient positioning using an electronic portal imaging device (EPID), cone-beam computed tomography (CBCT), or other available image-guided radiation therapy (IGRT) techniques to ensure any three-dimensional positional discrepancies are < 3mm. If 2D imaging is used in the proton therapy system, non-radiopaque metal spheres are recommended to serve as fiducials for image registration. but these should be removed before treatment.

Criteria for Discontinuing Interventions

Patients can withdraw from the trial at any time without penalty. If they withdraw before starting RT, they will receive standard care according to institutional guidelines. The date of withdrawal will be recorded as the day the study team acknowledges the notification. For patients who experience adverse events, the decision to continue or discontinue RT rests with the principal investigator (PI) or designated medical officer at the participating center, which will be based on an assessment of the event's severity and its potential impact on the patient's health and safety. All adverse events will be documented in the electronic Case Report Form (eCRF) and reported on time. Continued monitoring will be conducted post-withdrawal to ensure safety and proper care. The informed consent form provides details on the criteria for stopping an intervention or withdrawing from the trial.

Endpoints

Primary Endpoint

Acute radiation-induced toxicities: the incidence of Grade ≥ 2 acute toxicities at any time from the start of RT to 6 months after completion.

Secondary Endpoints

- Late radiation-induced toxicities: the incidence of late toxicities at any time from 6 months to 5 years after completion of RT, accessed according to RTOG criteria and CTCAE version 3.0.
- Cosmetic outcomes: for patients undergoing BCS, cosmetic results are evaluated using the Harvard Breast Cosmesis Scale, ranging from excellent (minimal or no difference compared to the untreated breast), good (slight difference in the size or shape), fair (obvious difference in the size or shape), to poor (marked change in size or shape).
- Local regional recurrence (LRR): the first recurrence in the ipsilateral breast, chest wall, or regional nodes (ipsilateral axillary, supraclavicular, or internal mammary nodes) confirmed by histology or cytology.
- Distant metastasis-free survival (DMFS): time from enrollment to the occurrence of distant tumor recurrence, or until the last follow-up.
- Invasive recurrence-free survival (IRFS): time from enrollment to the occurrence of invasive tumor recurrence, distant metastases, or until the last follow-up, including second invasive primaries of the breast.
- Overall survival (OS): time from enrollment to death from any cause or until the last follow-up.

Exploratory endpoints of the trial are quality of life using self-administered questionnaires EORTC QLQ-C30 and QLQ-BR23 (Chinese version).

Outcome Measures and Follow-Up

The schedule of enrollment, interventions, and assessments is detailed **in Table 1**. Any radiation-induced toxicities, tumor recurrence events, and deaths must be thoroughly documented in the eCRF. The radiation-induced toxicities are graded using RTOG criteria and CTCAE version 3.0. Survival events will be assessed by physical examination, serum test, ultrasound of the breast, regional nodes, and abdomen every 6 months, breast mammography, and chest CT scan annually after completion of RT.

Any additional examinations are at the discretion of clinicians. Lymphedema is defined as a ≥10% increase in arm circumference from baseline or the contralateral arm. Radiation-induced skin injuries and upper limb functional impairments are recorded with photographic and video evidence.

Data Collection and Management

Data collection is facilitated through an eCRF system established by the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. This online system comprises various forms to gather comprehensive data, including baseline information before enrollment, pre-treatment assessments, details of the RT plan, acute toxicities, follow-up reviews covering survival and toxicity at specified intervals, Quality of Life assessments using standardized questionnaires, and reporting forms for serious adverse events (SAEs). PI, ethical committees, and sponsors have unrestricted access to the database for real-time analysis and monitoring. Each participating center has access to its own data, with the leading investigators being responsible for data quality oversight. Upon trial completion, data quality and integrity are verified by specially trained personnel before the dataset is secured for analysis. All data generated by the study are treated with strict confidentiality. Patient identities will not be disclosed in any public reports or presentations of the study findings. The research center is obligated to retain all pertinent data for a minimum of 5 years post-study completion. Destruction of data is subject to approval by the ethical committee.

Calculation of Samples

The sample size for the trial is calculated using Power Analysis and Sample Size Software (2017) (NCSS, Kaysville, Utah, USA, www.ncss.com/software/pass).

Sample for the ARROW trial

The probability of a Type I error is 0.05, and the test power is 80%. The acceptable threshold (δ) is 10%. Previous studies have shown that the incidence of acute radiation-induced toxicity in patients receiving conventional fractionated RNI is 45% [22, 24, 25]. Assuming the incidence of grade 2 or higher acute radiation-induced toxicity is less

than 55%, and adopting a non-inferiority test, then a total of 177 patients need to be enrolled. In consideration of an expected dropout rate of 10%, the sample size for this study is determined to be 197 cases.

Statistical Analysis

All efficacy and safety analyses will be based on the intention-to-treat principle, and a per-protocol analysis will be performed for the primary endpoint. Acute and late toxicities will be summarized by frequency and severity based on their association with the protocol treatment. To account for differences in toxicity profiles between RT modalities, patients were stratified into two subgroups (IMRT and proton therapy). This stratification ensured independent evaluation of adverse events, while controlling for confounding variables such as OARs dosimetry and baseline patient characteristics. Cumulative proportions of time to survival endpoints such as DMFS, IRFS, and OS will be described using the Kaplan-Meier method. Severe radiation-related toxicity events will be listed individually. The t-test will be used for the comparison of continuous variables. Statistical analysis will be performed using SPSS software version 21.0 (IBM Corporation, Armonk, NY, USA).

Monitoring

The trial is overseen by a Trial Steering Committee (TSC), with leading investigators from all participating centers. The TSC ensures that the trial follows the protocol and ethical guidelines. Study coordination, monitoring, data acquisition, management, and statistical analysis are conducted by a team of statisticians at Ruijin Hospital affiliated with Shanghai Jiao Tong University School of Medicine. This team ensures the integrity and quality of the data collected throughout the trial. An Independent Data Safety and Monitoring Committee (DSMC) is established to oversee the safety and data quality of the trial. The DSMC monitors the progress of the trial, reviews safety data, and assesses the quality of the data. Using the available data, the DSMC makes recommendations to the TSC regarding the continuation of the trial.

Adverse Event Management

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease that occurs during the trial, regardless of whether it is related to RT. Serious adverse events (SAEs) must be reported to the ethical committee within 24 hours of the PI's awareness. If an SAE occurs, all anti-tumor treatments must be halted immediately, and the patient must be monitored until the event is resolved or stabilized, even if it leads to the patient's withdrawal from the study.

The details of SAEs, including the time of onset, severity, expectedness, duration, measures taken, and outcomes, must be meticulously recorded in the eCRF. Reporting of all AEs to the ethical committee and the PI is mandatory at regular intervals, typically every 6 to 12 months.

Ethics and Dissemination

The clinical trial has been approved by the Ethical Committee of Ruijin Hospital affiliated with Shanghai Jiao Tong University School of Medicine, as well as by the ethical committees of all participating centers. This demonstrates our commitment to conducting research that follows the highest ethical standards. Any changes to the protocol will be carefully documented and submitted for ethical committee review and approval before being implemented. This strict oversight ensures that all trial modifications are in the best interest of the participants and the scientific integrity of the study. The study follows the Declaration of Helsinki and adheres to Good Clinical Practice (GCP) guidelines to ensure the protection of human rights, safety, and well-being of all trial participants.

Participants will provide informed consent before enrolling to ensure full awareness of the study's objectives, procedures, benefits, and risks. Upon completion of the research, findings will be prepared for submission to peer-reviewed journals. Authorship will be reserved for individuals who have made significant contributions to the study's design, conduct, and analysis. The final clinical study reports and their summaries will be disseminated to the local ethical committees, institutes, and sponsors involved in the protocol, ensuring transparency and accountability in the research

process.

Patient and Public Involvement

In the design, execution, reporting, and dissemination of our research, we have not engaged patients or members of the public. The research team developed and conducted the study without direct input from these groups.

Discussion

Short-course RT offers several advantages, including reduced use of scarce resources, realized work time and cost savings, increased throughput, reduced waiting times, and decreased non-medical expenses for patients [26]. Following the publication of the 5-year outcomes from the Fast-Forward trial, there has been a surge of interest in one-week regimens, prompting the initiation of multiple studies (Table S6). In these ongoing trials, there are significant variations in the specifications for tumor bed boost and IMNI. Our trial innovates by extending the application of ultra-hypofractionated regimens to sequential tumor bed boosts and IMNI. The ultra-hypofractionated tumor bed boost limits the RT course to a maximum of 1.5 weeks, with a single fractional dose consistent with WBI and RNI, offering a more convenient clinical strategy. The trial also allows the enrollment of patients who have undergone breast reconstruction, received neoadjuvant treatment, and those with positive sentinel lymph nodes (SLN) but no axillary lymph node dissection (ALND). This provides a better representation of the real-world patient population.

The main concern regarding IMNI is the increased risk of cardiac and pulmonary toxicity, especially for left-sided patients. Due to reduced cardiac and lung doses with the use of advanced RT techniques, the overall benefits of IMNI have been demonstrated in multiple prospective clinical trials [2, 4-6, 20, 21]. The MA20 study showed a notable improvement in disease-free survival (DFS) for the RNI group, including IMNI, compared to the group without RNI [2]. Echoing these findings, the EORTC 22922/10925 study revealed a significant reduction in breast cancer mortality and any recurrence among patients who received RNI, including IMNI [21, 27].

Furthermore, the DBCG-IMN study substantiated the positive impact of IMNI on reducing the risk of distant recurrence and breast cancer mortality, thereby enhancing long-term survival [5, 28]. Of note, no excess cardiac mortality with IMNI was observed in these trials [2, 5, 21, 27-29]. In light of these findings, the ARROW trial mandates IMNI for all participants, with the expectation that it will yield data on the safety of the ultra-hypofractionated regimen for RNI, including IMNI. Considering the concerns regarding cardiac and pulmonary toxicity, our study protocol included follow-up assessments of cardiac function using electrocardiography and echocardiography, as well as monitoring for radiation pneumonitis using chest CT scans. This can provide more comprehensive safety data for the one-week regimen of IMNI.

In addition, the ARROW trial allows for the inclusion of patients with positive SLNs but no ALND. The pivotal studies such as Z0011, AMAROS, IBCSG 23–01, and SENOMAC have demonstrated that omission of ALND is non-inferior to ALND in terms of oncologic outcomes for patients with 1-2 positive SLNs [30-33]. Driven by the findings from these trials, an increasing number of patients with positive SLNs are being spared from ALND in clinical practice. Axillary RT, as demonstrated by the AMAROS trial, was non-inferior to ALND in terms of overall survival (OS), DFS, and locoregional control. Furthermore, axillary RT showed a reduction in the incidence of lymphedema compared to ALND [30]. In a prospective screening trial, Naoum et al [34] found that the ALND-only group had a significantly higher risk of breast cancer-related lymphedema compared to the group receiving SLN biopsy plus RNI (24.9% vs. 10.7%, $p = 0.02$). However, the impact of ultra-hypofractionated RNI, including axillary RT, on oncologic outcomes and radiation-induced toxicities such as lymphedema in these patients remains to be determined. The ARROW trial aims to provide preliminary data on the feasibility of ultra-hypofractionated RNI in patients with SLNs but no ALND.

Tumor bed boost has been shown to reduce the local recurrence in high-risk patients undergoing BCS [35]. However, determining the optimal fractionation scheme for tumor bed boost in the era of short regimens remains a topic of debate. The Fast-Forward trial adhered to a conventional fractionation approach, prescribing tumor bed boosts of 10 Gy or 16 Gy in 2 Gy fractions sequential to WBI [19]. Not all ongoing

one-week regimen trials have disclosed detailed protocols for tumor bed boost. There are also variations in the dose fraction for the tumor bed boost. For instance, the HYPORT trial (NCT03788213) of WBI or chest wall irradiation with or without RNI permits both a simultaneous integrated boost (SIB) of 32 Gy in 5 fractions and a sequential boost of 12 Gy in 4 fractions. Another trial of WBI (NCT05586256) offers an SIB of 30 Gy in 5 fractions or a sequential boost of 7.6 Gy in 2 fractions. Our trial diverges from other single-week regimen trials by administering a sequential tumor bed boost of 10.4 Gy in 2 fractions, aligning with the single fractional dose used for WBI and RNI to make it convenient for clinical practice. While SIB offers advantage in reducing overall treatment duration, its safety and efficacy in the context of single-week ultrahypofractionation remain uncertain. Within the context of ultrahypofractionated regimen, incorporating SIB would further increase the fractional dose delivered to the tumor bed, whether this more aggressive approach will increase the risk of late toxicities, such as skin fibrosis and poor cosmetic outcomes is uncertain as long-term results are insufficient. Considering these factors, at this stage, we prioritized validating the safety of ultrahypofractionation with a sequential boost which maintains the ultrahypofractioned size before exploring the feasibility and safety of SIB. We expect to contribute evidence on the safety of a sequential ultra-hypofractionated tumor bed boost and pave the way for future randomized controlled trials evaluating SIB in this context.

One of the critical challenges in implementing ultra-hypofractionated regimens is the high demand for precision in both patient positioning and dose delivery. To address this, we employed daily CBCT imaging, ensuring positional errors in three dimensions do not exceed 3mm. Additionally, our trial utilizes IMRT and proton therapy to minimize the dose of OARs as much as possible, particularly for the left-sided IMNI. The decision to utilize proton therapy or IMRT in this study was based on a structured, patient-centered framework. Proton therapy was prioritized for left-sided IMNI, patients at high risk of radiation-induced toxicity or cases where IMRT plans could not meet heart or lung dose constraints. IMRT was uniformly employed with strict adherence to predefined dose constraints when proton therapy was unavailable due to

institutional limitations (e.g., lack of proton facilities) or patient-specific barriers (e.g., insurance denial despite dosimetric superiority). Patients with IMRT plans exceeding tolerance limits after optimization were excluded and offered alternative regimens. This dual-tiered approach highlights the real-world complexities of integrating state-of-the-art RT technologies, balancing dosimetric superiority against resource limitations and healthcare inequities. Incorporating daily imaging-guided RT and state-of-the-art RT techniques has the potential to enhance the safety of the ultra-hypofractionated regimen. The technical details in our protocol could provide a framework for the broader clinical adoption of ultra-hypofractionated regimens in the future.

The ARROW trial holds significant importance in exploring the safety and efficacy of ultra-hypofractionated regimens for RNI including IMN and sequential tumor bed boost in early breast cancer patients. The results of our trial are expected to pave the way for the broader adoption of ultra-hypofractionated regimens among postoperative RT breast cancer patients. Furthermore, the IMRT and proton therapy used in our trial can provide more favorable dose distributions for the target volume and OARs, while offering data for implementing an ultra-hypofractionated regimen with these state-of-the-art RT techniques. After confirming the feasibility and safety of this ultrahypofractionated regimen in the ARROW trial, our team plans to conduct a phase III randomized controlled trial, which will comprehensively evaluate both the efficacy and safety of the one-week regimen in RNI.

Declarations

Acknowledgements

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Authors' contributions

LC and JC design the original protocol for the study. JX and SZ contributed to study management and drafted the manuscript. WQ performed the sample size calculation

and data analysis. All authors participated in enrollment and follow-up of patients. All authors read and approved the final manuscript. Jiayi Chen is the guarantor.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of Shanghai Jiao Tong University School of Medicine affiliated Ruijin Hospital (IEC approval number for ARROW 1.3: 2020-167-4, Date:2024-09-13). Written informed consent is obtained from all participants before study participation. See **Additional file 1** for the SPIRIT checklist of the study protocol.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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Figure legend

Figure 1 Study design

Abbreviations: Fx=fractions

Table 1 Schedule of enrollment, interventions, and assessments

	STUDY PERIOD							
	Pre-radiotherapy	Interventions: Radiotherapy		Post-radiotherapy				
TIMEPOINTs	**baseline**	**1w**	**2w**	**4w**	**6m**	**12m**	**18m**	**2y**
ENROLLMENT:								
Eligibility screening	X							
Informed consent	X							
INTERVENTIONS:								
Ultra Hypofractioned regimen		X	X					
ASSESSMENTS:								
History and Physical Examination	X	X	X	X	X	X	X	X
Chest CT scan	X[a]					X		X
Mammography						X		X
Ultrasound for Breast and regional nodes	X				X	X	X	X
ECG	X				X	X	X	X
Echocardiography	X				X	X	X	X
Cosmetic outcomes for BCS	X			X	X	X	X	X
Quality of life	X			X	X	X	X	X

[a] Simulation CT is acceptable

Abbreviations: CT = Computed Tomography; ECG = Electrocardiogram; BCS = Breast-Conserving Surgery; w=week, m=month; y=years

Annual assessments will be conducted 2 years subsequent to the completion RT.

the study design

1058x253mm (96 x 96 DPI)

Additional File

Page2:

Table S1 Anatomical boundaries of Chest wall/whole breast CTV

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Table S2 Anatomical boundaries of CTV for regional nodes

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Table S3 Tumor bed boost contours

Page6-7:

Table S4 Dosimetric coverage for target volume

Page8-9:

Table S5 Dose constraints for OARs

Page10-13:

Table S6 The ongoing trials on the one-week regimen for WBI alone and for RNI in early breast cancer

Table S1. Anatomical boundaries of chest wall and whole breast CTV

	Chest wall	Whole breast
Cranial	Guided by palpable /visible signs; if appropriate guided by the contralateral breast; maximally up to the inferior edge of the sternoclavicular joint	Upper border of palpable /visible breast tissue; maximally up to the inferior edge of the sternoclavicular joint
Caudal	Guided by palpable/visible signs; if appropriate guide by the contralateral breast	Clinical reference; last caudal CT slice with visible breast
Anterior	Skin	5mm under skin surface
Posterior	Include pectoralis muscles, chest wall muscles, excluding ribs	Exclude pectoralis muscles, chest wall muscles, ribs
Lateral	Guided by palpable/visible signs; if appropriate guide by the contralateral breast. Usually anterior to the mid-axillary line, excludes lattices dorsi muscle	Lateral breast fold, anterior to the lateral thoracic artery
Medial	Lateral to the medial perforating thoracic internal vessels; maximally to the edge of the sternum	Lateral to the medial perforating thoracic internal vessels; maximally to the edge of the sternum

Notes: For patients with stage III according to AJCC 8th edition, the posterior of the whole breast can extend to the rib interface.

Table S2. Anatomical boundaries of regional nodal CTV

	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Medial Supra-clavicular	Caudal to the cricoid cartilage	Junction of brachioceph-axillary veins / Caudal edge clavicle head	Posterior edge of sternocleidomastoid muscle	Posterior surface of internal carotid artery or anterior surface of scalene muscles	Medial border of clavicle head 5 mm below the skin surface	Medial border of internal carotid vessels
Lateral Supra-clavicular*	Caudal to the cricoid cartilage	Junction of Brachioceph. - axillary veins. /Caudal edge clavicle head	Posterior surface of internal carotid artery or anterior surface of scalene muscles	At the trapezius	Medial border of clavicle head 5mm below the skin surface	At the longus coli
Internal mammary	Junction of Brachioceph-axillary veins.	Cranial side of the 4rd rib (in selected cases 5th rib)	Ventral limit of the vascular area	Pleura	7mm from internal mammary vessels	7mm from internal mammary vessels
Axilla-level I	Below the humeral head	At the point where the pectoralis major inserts on the ribs (around 4th to 5th rib)	At posterior pectoralis major & minor muscles	An imaginary line anterior to the surface of latissimus dorsi muscle, subscapularis muscle and teres major muscle	Cranially up to an imaginary line between the major pectoral and deltoid muscles and further caudal up to a line between the major pectoral and latissimus dorsi muscles	Lateral border of pectoralis minor musle
Axilla-level	Insertion point	The caudal border of	Pectoralis minor muscle	Anterior border of ribs	Lateral edge of pectoralis	Medial edge of

II	of pectoralis minor muscle	the pectoralis minor muscle		and serratus anterior	minor muscle	pectoralis minor muscle
Axilla-level III	Pectoralis minor muscle insert on Coracoid	Axillary vessels cross medial edge of pectoralis minor muscle	Posterior surface of pectoralis major muscle	Anterior border of ribs or posterior border of subclavian or axillary vessels	Medial border of pectoralis minor muscle	Lateral border of clavicle, ribs, junction of brachioceph-axillary veins.

Notes:

1) The regional nodal CTV target volume should include the medial supra-clavicular, axilla-level III, undissected axilla-level I and internal mammary lymph nodes.
2) The inclusion of axilla-level I and II in the regional nodal CTV is at the discretion of radiation oncologists based on the clinical treatment indications. The rotter's nodes are included in the CTV target volume of axilla-level II.
3) For N2, N3, or high-risk N1 patients, it is recommended to include the lateral supra-clavicular nodes in the regional nodal CTV.
4) When the tumor is in the inner lower quadrant, the caudal border of internal mammary nodes is recommended to extend to the cranial side of the 5th rib.

Table S3. Tumor bed GTV and CTV contours

GTV	Includes seroma and/or surgical clips
CTV	GTV with a margin of 1 cm in all directions and without exceeding CTV of the whole breast

Abbreviations: GTV=gross tumor volume, CTV=clinical target volume

Table S4. Dosimetric coverage for target volume

Target volume		Requirements
PTV of chest wall/whole breast and RNI	Per Protocol	D95%>42.5Gy
	Acceptable variation	D90%>42.5Gy
	Per Protocol	V28Gy<20%
	Acceptable variation	V29Gy<20%
	Per Protocol	V25Gy>99%
	Acceptable variation	V24Gy>99%
CI for PTV of chest wall/whole breast and RNI	Per Protocol	≥0.95 and ≤2
	Acceptable variation	≥0.85 and ≤2.5
Tumor bed PTV	Per Protocol	D95%>50.4Gy
	Acceptable variation	D90%>50.4Gy
	Per Protocol	V39Gy<5%
	Acceptable variation	V40Gy <5%
	Per Protocol	V35Gy >99%

	Acceptable variation	V34Gy ≥ 39%
CI for Tumor bed PTV	Per Protocol	≥0.95 ≥2.5
	Acceptable variation	≥0.9 ≥3

Notes:

1) When evaluating the treatment plan of chest wall/whole breast with RNI, tumor bed boost doses should not be considered.
2) CI=Conformity index, the volume covered by 95% of the prescription dose / PTV volume
3) For evaluation of IMRT plan: a) The whole breast CTV is expanded by 5-8mm in three dimensions to form the PTV. The PTV is limited to 5mm below the skin and the surface of the pectoral muscle or chest wall to form the whole breast PTV_eval for IMRT plan evaluation; 2) The chest wall and regional nodal CTV is expanded by 5-8mm in three dimensions to form an integrated PTV; Limit the PTV to the skin as the anterior boundary and the chest pleura as the posterior boundary to form the PTV_eval for plan evaluation.
4) For evaluation of proton plan: a) the dosimetric coverage of the CTV is evaluated; b) The chest wall CTV is recommended to retract 5mm from skin; c) If the chest wall is very thin, 3mm can be considered.

Table S5. DVH constraints for OARs

OARs	The ARROW trial		
	Dosimetric parameter	Per protocol	Acceptable variation
Heart for left-sided breast cancer	Mean	<3Gy	<3.5Gy
	V15Gy	<10%	<15%
	V4Gy	<20%	<25%
	N/A	N/A	N/A
Heart for right-sided breast cancer	Mean	<1Gy	<1.5Gy
	V2Gy	<15%	<20%
Ipsilateral Lung	Mean	<7.5Gy	<8Gy
	V4Gy	<45%	<50%
	V10Gy	<30%	<35%
	V15Gy	<20%	<23%
Contralateral lung	Mean	<1Gy	<1.5Gy
	V2Gy	<10%	<15%
Spinal cord	Max	<20Gy	N/A
Ipsilateral Humeral head	Mean	<10Gy	<11Gy

Contralateral breast	Mean	<3.5Gy	<5Gy
Brachial plexus	D0.1cc	<27Gy	<28Gy
Esophagus	D1cc	< 26Gy	< 27Gy
	D 0.01cc	< 27Gy	< 28Gy
Thyroid	Mean dose	< 10Gy	< 11Gy
Skin ring	V2Gy	<10%	<15%

Table S6. The ongoing trials on the one-week regimen for WBI alone and for RNI in early breast cancer

NCT Number	Country	Age (years)	Start year	Randomized	Enrolled patients	Reconstruction	Tumor bed Boost	IMNI	Study group	Control group	Sample size	Primary Endpoint	Status
WBI alone													
NCT05586256	Italy	18-99	2021	No	Indicated for WBI	N/A	Optional, SIB of 30Gy/5Fx or sequential 7.6Gy/ 2Fx	N/A	26Gy/5Fx/1w	N/A	300	Acute and chronic toxicity	Recruiting
NCT05318274	Mexico	≥18	2021	Yes	BCS, pTis-T2, N0	N/A	Study group: No boost; Control group: SIB of 48Gy/16Fx in high risk patients	N/A	26Gy/5Fx/1w	42.5Gy/16Fx/1w	72	Local control	Recruiting
NCT04669873	Brazil	50-90	2021	Yes	BCS, unifocal disease, T＜3cm，pN0, negative LVSI, Grade 1-2,	N/A	No	N/A	Group1: 26Gy/5Fx/1w for WBI Group2: 26Gy/5F	40Gy/15Fx/3w for WBI	36	Local recurrence	Recruiting

					margin＞2mm				x/1w for PBI				
NCT05417516	Canada	≥50	2023	Yes	BSC, negative margin, N0	N/A	No	N/A	26Gy/5Fx/1w for PBI	26Gy/5Fx/1w for WBI	910	Local recurrence	Recruiting
RNI													
NCT03788213	India	≥18	2019	Yes	BCS, or after NAC, or mastectomy with pT3/T4 or pN2 or pT0-2pN0-1 with a Cambridge Score of 3 or more	Yes	Study group:SIB of 32Gy/5Fx, or sequential 12Gy/4Fx; Control group: SIB of 48Gy/15Fx, or sequential 12Gy/4Fx	Based on institutional policy	26Gy/5Fx/1w for WBI/Chest wall, and RNI in N+ or after NAC	40Gy/15Fx/3w for WBI/chest wall and RNI in N+ or after NAC	2100	Locoregional recurrence rate	Recruiting
NCT04648904	United States	≥30	2020	No	mastectomy with reconstruction; pathologic T0N1a-2a, T1N1a-2a,	Yes	Optional chest wall boost of 5.2 Gy for 1-2 fractions or 2.5 Gy for 1-4 fractions	Not mentioned	26Gy/5Fx/1w	N/A	72	Local and regional recurrences	Recruiting

					T2N1a-2a, T3N0-2a, all M0								
NCT04443413	United States	≥18	2020	Yes	BCS or mastectomy; clinical or pathologic T1-T4c, N0-3, M0; indicated for RNI	Not mentioned	Optional Study group: SIB of 5-fraction; Control group: 4-fraction boost of x-ray therapy	Not mentioned	proton therapy over 5 fractions	x-ray therapy over 5 fractions	146	Complication rate	Recruiting
NCT04228991	Canada	≥18	2021	Yes	BCS or mastectomy; pT3N0, pT1-3N1-2; Or NAC with cT3N0, cT1-3N1-2 and ypT0-3N0-2	No	Not mentioned	Not mentioned	26Gy/5Fx/1w	40Gy/15Fx/3w	588	Lymphedema	Recruiting
NCT04472845	India	≥18	2021	Yes	BCS or mastectomy; pT3-4pN2-3 M0; NAC with clinical	Tissue expanders with distant metal ports	Study group: SIB of 34Gy/5Fx or sequential 8Gy/2Fx/2d; Control	for patients with T3-4 central and	26Gy/5Fx/1w	34Gy/10Fx/2w	1018	Locoregional control	Recruiting

					stage III or ypN+	are allowed	group: SIB of 42Gy/10fx/2w or sequential 8Gy/2Fx/2d	inner quadrant lesions and patients with N2					
NCT05150535	Egypt	≥45	2021	Yes	BCS or mastectomy; TxN1-3M0, T0-2N2-3M0, T3-4N0-3M0; Or LABC with NAC	Not mentioned	Study group: SIB of 32Gy/5Fx or sequential 12Gy/ 4Fx; Control group: SIB of 48Gy/15Fx, or sequential 12Gy/4Fx	For patients with N2-3	26Gy/5Fx/1w for WBI/Chest wall, and RNI in N+ or after NAC	40Gy/15Fx/3w for WBI/Chest wall and RNI in N+ after NAC	100	Acute and chronic grade 2 toxicity or higher	Unknown
NCT05665920	Brazil	≥18	2022	Yes	BCS; pT1-3 and pN1-3a; with indication of RNI	N/A	Not mentioned	No	26Gy/5Fx/1w	40Gy/15Fx/3w	36	Locoregional recurrence	Recruiting

Abbreviations: WBI = Whole Breast Irradiation; RNI = Regional Nodal Irradiation; IMNI = Internal Mammary Nodal Irradiation; N/A = Not Applicable; SIB = Simultaneous Integrated Boost; w = week; d = days; BCS = Breast-Conserving Surgery; LVSI = Lymphovascular Space Invasion; PBI = Partial Breast Irradiation: NAC = Neoadjuvant Chemotherapy; LABC = Locally Advanced Breast Cancer.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Page	Section/item	Item No	Description
	Administrative information		
1	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
3	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
		2b	All items from the World Health Organization Trial Registration Data Set
19	Protocol version	3	Date and version identifier
19	Funding	4	Sources and types of financial, material, and other support
1,18	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
1		5b	Name and contact information for the trial sponsor
18		5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
14		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
	Introduction		

4	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
Not applicable		6b	Explanation for choice of comparators
5	Objectives	7	Specific objectives or hypotheses
5	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
	Methods: Participants, interventions, and outcomes		
5	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
6-8	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
5,8-10	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
10		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
6,12		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
8		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial

11-12	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
12,24	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
6,12	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
	Methods: Assignment of interventions (for controlled trials)		
	Allocation:		
Not applicable	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Not applicable	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

	Not applicable	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
	Not applicable	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	Not applicable		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
		Methods: Data collection, management, and analysis		
	12	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	6,12		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
	12	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
	13-14	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

13-14		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
13-14		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
14	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
Not applicable		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
14	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
14	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
15,19	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
15	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

6,19	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
Not applicable		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
12	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
19	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
12-14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
14-15	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
15	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
15		31b	Authorship eligibility guidelines and any intended use of professional writers
Not applicable		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
	Appendices		
19	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates

Not applicable	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.