

HOW TO READ AND DISSECT TRIAL AND ITS RELEVANCE IN CLINICAL PRACTICE

• By

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TITLE — WHY IT MATTERS

TELLS YOU THE QUESTION + DESIGN + COMPARATOR AT A GLANCE.

JOURNAL — WHY IT MATTERS

•Indicates peer-review rigor, reporting standards, and visibility.

HELPS JUDGE TRUSTWORTHINESS (indexed in MEDLINE/PubMed, reputable editorial board; not predatory).

CONTEXT FOR AUDIENCE & SCOPE (oncology specialty vs general medical; methods journals).

Beware **supplement issues** (may have different review rigor).

AUTHORS — WHY THEY MATTER

CHECK EXPERTISE & ROLES (specialty fit; presence of a **biostatistician**; multicentre collaborators).

REVIEW AFFILIATIONS (academic vs industry) and **conflicts of interest (COI)** disclosures.

SENIOR/CORRESPONDING AUTHOR CREDIBILITY → clues to **methodological rigor** and accountability.

YEAR OF PUBLICATION — why it matters

Places evidence in time (recency, follow-up, current relevance).

FAST-Forward: 2020 (5-year results). → Modern RT era; adequate medium-term outcomes for decision-making.

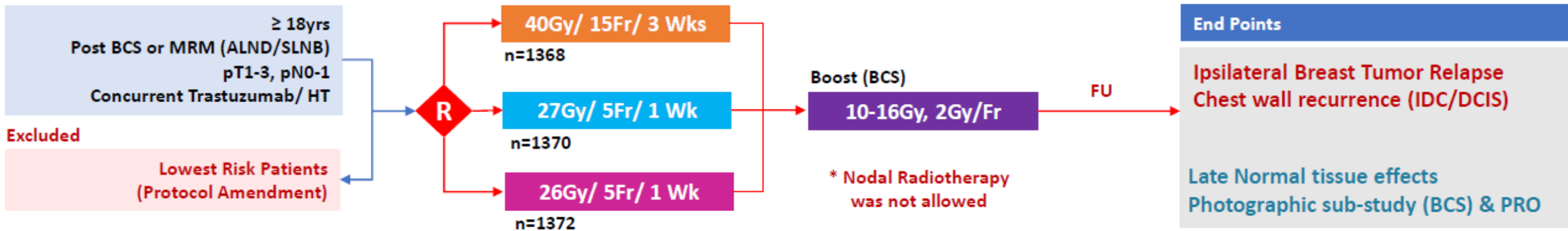
1. Title :-shows **design + PICO** clearly? If not, proceed cautiously.
2. Authors have **relevant specialty + strong expertise** and transparent COI?
3. Journal is **reputable & indexed** and follows reporting standards?
4. Year aligns with **current practice/guidelines** and has adequate follow-up?
- 5..

IF ALL "YES," INVEST TIME IN FULL APPRAISAL; IF NOT, BE SKEPTICAL OF CLINICAL ADOPTION

Hypofractionated breast radiotherapy for 1 week Vs 3 weeks (FAST-Forward): 5-yr efficacy and late normal tissue effects results

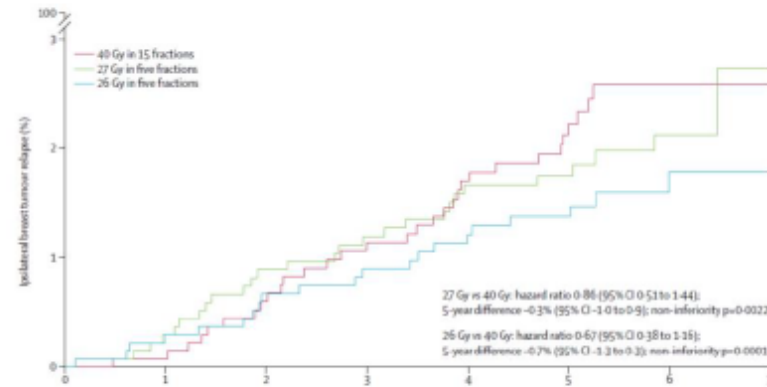
Lancet 2020
Adrian M Brunt, Joanne S Haviland
Multicentre Phase 3 RCT

To identify a 5 fraction/ 1 week schedule that is non-inferior to standard 15-fraction regimen



Median FU 71.5 month, Compliance to allocated treatment 99%

40Gy/15Fr	27Gy/5Fr	26Gy/5Fr
IBTR – HR (Vs 40Gy/15Fr)	0.86	0.67
5Yr IBTR (2.1%)	1.7%	1.4%
Regional Relapse (1%)	0.8%	0.7%
Normal Tissue Effect* 5yrs 9.9%	15.4% p – 0.0003	11.9% p – 0.17
OR (Vs 40Gy/15Fr)	1.55 p<0.0001	1.12 p - 0.20



PRO & Photographic Sub-study - 27Gy had significantly higher risk of changes compared to 40Gy or 26Gy

Demonstrated non-inferiority of either regimen to 40Gy/15Fr for IBTR at 5yrs

Similar Normal tissue effect noted for 26Gy and 40Gy at 5yrs of follow-up

Estimated α/β value for tumor control – 3.7Gy assuming no effect of time

5Fr regimen is convenient and substantially less expensive for patients and health service

* Most Common – Breast Shrinkage

CONCLUSION: 26Gy/5Fr/1wk is non-inferior to 40Gy/15Fr in terms of tumor control and normal tissue effect

TITLE — why it matters

Tells you the **question + design + comparator** at a glance.

FAST-Forward: “Hypofractionated breast radiotherapy for 1 week versus 3 weeks... phase 3, non-inferiority.”

→ You immediately know it’s a head-to-head RCT testing **1-week vs 3-week** schedules.

AUTHORS — WHY THEY MATTER

Signal **expertise, trial credibility, and conflicts.**

FAST-Forward: Brunt

multicentre RT

→ Rea

UK

CLINICAL SIGNIFICANCE (from FAST-Forward)

26 Gy in 5 fractions (1 week) is non-inferior to 40 Gy in 15 fractions (3 weeks) for local control, with **similar late effects** → practical, patient-friendly standard for suitable early breast cancer.

27 Gy/5: higher late normal-tissue effects → generally **avoid**

ing standards,

Lancet.

standards; widespread clinical

→ findings are more likely to inform **practice/guidelines.**

YEAR OF PUBLICATION — why it matters

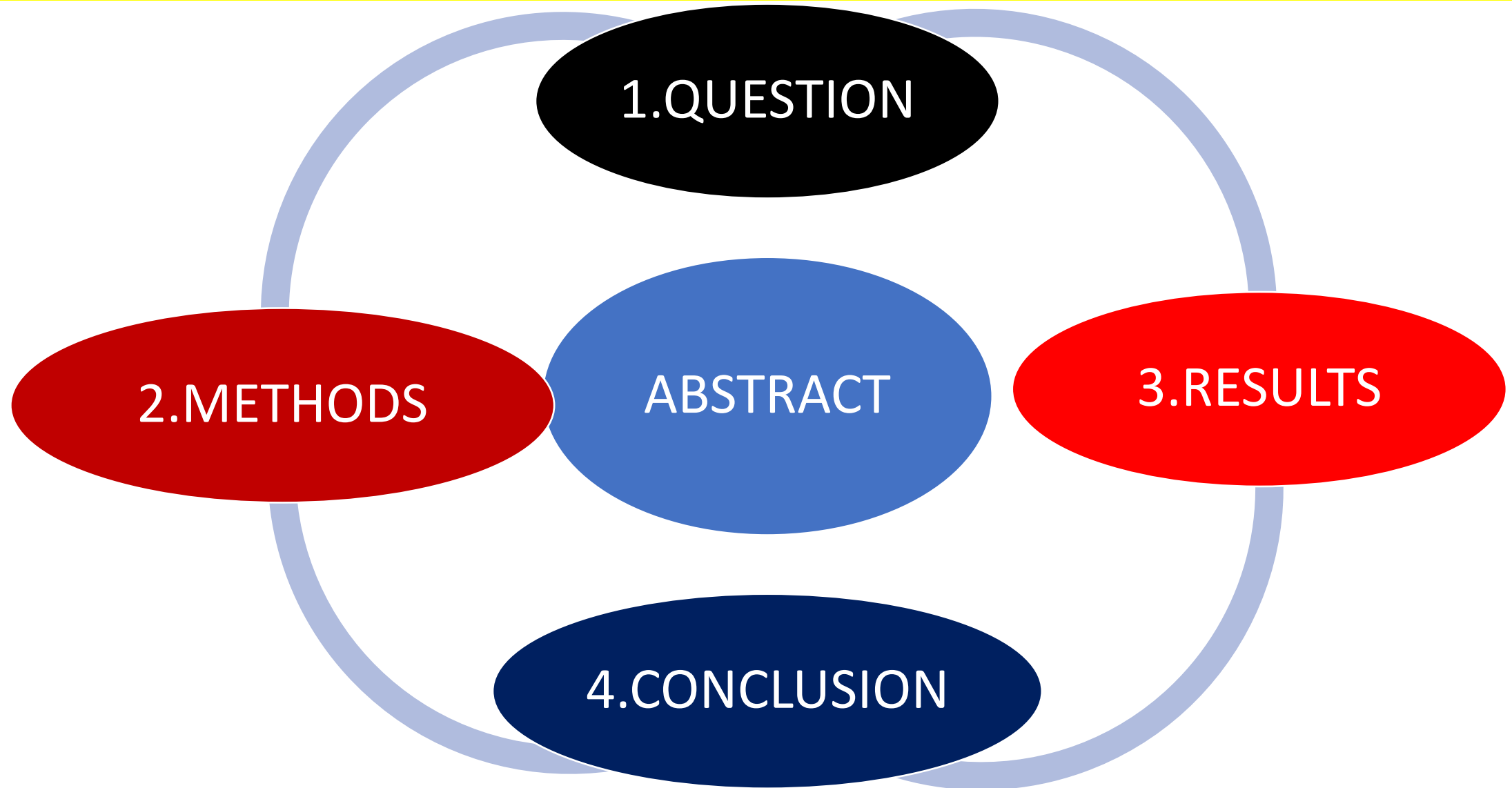
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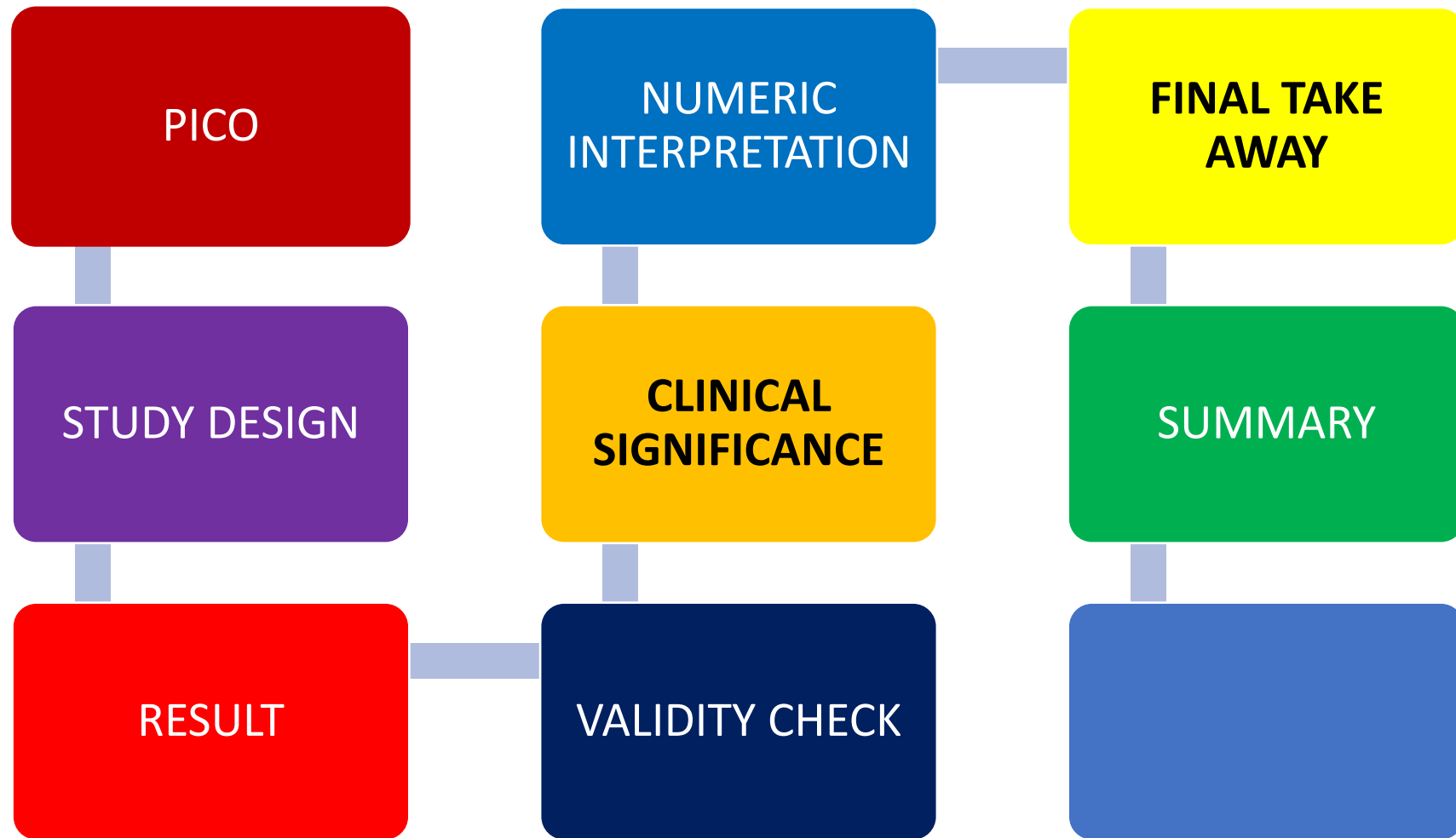
FAST-Forward: 2020 (5-year results). → Modern RT era; adequate medium-term outcomes for decision-making.

READ THE ABSTRACT CAREFULLY:-

ABSTRACT GIVES A SUMMARY: QUESTION, METHODS, KEY RESULTS, AND CONCLUSION.

•BE CAUTIOUS—ABSTRACTS CAN BE BIASED OR OMIT LIMITATIONS.

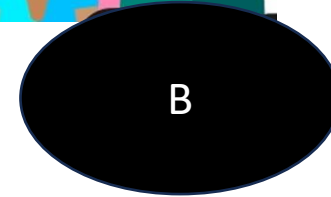
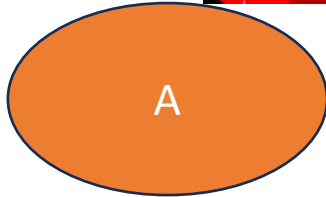




IDENTIFY THE RESEARCH QUESTION (PICO FORMAT)



•P: POPULATION



•I: INTERVENTION

•C: COMPARISON



•O: OUTCOME



FAST FORWARD TRIAL Identify the PICO

- **POPULATION (P)**: Women with early-stage invasive breast cancer after breast-conserving surgery or mastectomy.
- **INTERVENTION (I)**: Hypofractionated whole-breast/chest wall radiotherapy using:
 - 26 Gy in 5 fractions (over 1 week), OR
 - 27 Gy in 5 fractions (over 1 week).
- **COMPARATOR (C)**: Standard hypofractionated RT (40 Gy in 15 fractions over 3 weeks).
- **OUTCOME (O)**:
 - Primary: Local tumor control (ipsilateral breast/chest wall recurrence at 5 years).
 - Secondary: Toxicity, cosmesis, safety.

WHAT QUESTION IS THE ABSTRACT ANSWERING?:- :

1-week/5-fraction adjuvant schedule **NON-INFERIOR FOR LOCAL CONTROL AND AS SAFE AS STANDARD** 40 Gy/15f (3 weeks) after surgery for early breast cancer.

2) STUDY DESIGN (FROM THE ABSTRACT)

: Multicentre, phase 3, randomised non-inferiority trial at 97 UK hospitals.

3) POPULATION & SCOPE: Adults with invasive breast cancer pT1–3, pN0–1, M0 after BCS or mastectomy.

4) RANDOMISATION:- Arms: 40 Gy/15f (3 wks) vs 27 Gy/5f (1 wk) vs 26 Gy/5f (1 wk) to whole breast/chest wall; open-label.

5) PRIMARY ENDPOINT: Ipsilateral breast tumour relapse (IBTR). NI margin: $\leq 1.6\%$ absolute excess at 5 y (critical HR 1.81). Safety: Normal-tissue effects by clinician, patient, and blinded photographs. Trial registered (ISRCTN19906132). PubMed

3) RESULTS (WHAT DID THEY FIND?) N RANDOMIZED:

4096 (40 Gy n=1361; 27 Gy n=1367; 26 Gy n=1368).

Median follow-up 71.5 mo.

IBTR events: 31 (40 Gy), 27 (27 Gy), 21 (26 Gy).

HR vs 40 Gy: 0.86 (27 Gy); 0.67 (26 Gy).

5-y IBTR: 2.1% (40 Gy), 1.7% (27 Gy), 1.4% (26 Gy).

NI p-values: 27 Gy p=0.0022; 26 Gy p=0.00019 (met NI).

Toxicity (1–5 y clinician-assessed OR vs 40 Gy): 1.55 (27 Gy, \uparrow effects, p<0.0001); 1.12 (26 Gy, NS, p=0.20).

Patient/photographic assessments echoed: 27 Gy higher, 26 Gy similar. PubMed4)

INTERPRETATION (AUTHORS' TAKEAWAY) 26 Gy/5f (1 wk) is non-inferior for local control and as safe to 5 y; supports a 1-week standard for suitable patients.

CLEARLY STATES DESIGN, ENDPOINTS, NI MARGIN, AND KEY EFFECT SIZES (HRS, ABSOLUTE 5-Y RISKS) PLUS TOXICITY— ENOUGH TO JUDGE PROMISE AND SAFETY AT A GLANCE.

READ

TITLE, AUTHOR, JOURNAL, YEAR OF PUBLICATION

IDENTIFY THE RESEARCH QUESTION

ABSTRACT

STUDY DESIGN

DISSECT

SIGNALS PICO & DESIGN, SCOPE/SETTING
EXPERTISE & ROLES, REVIEW AFFILIATIONS
SENIOR/CORRESPONDING AUTHOR CREDIBILITY HELPS JUDGE TRUSTWORTHINESS,
peer-review rigor, reporting standards, and visibility
RECENCY, FOLLOW-UP, CURRENT RELEVANCE).

PICO

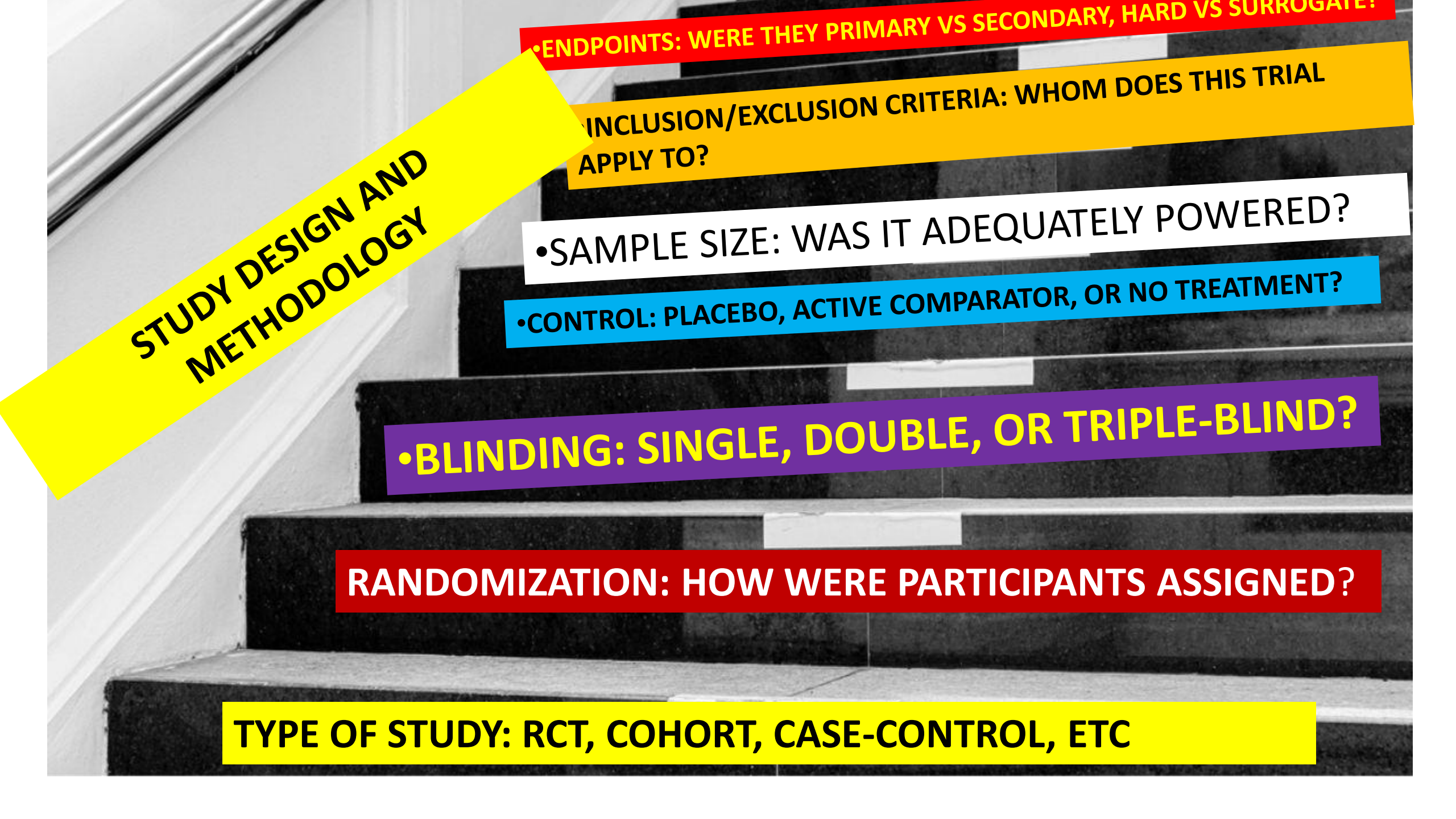
ABSTRACT GIVES A SUMMARY: QUESTION, METHODS, KEY RESULTS, AND CONCLUSION

TYPE OF

STUDY, RANDOMIZATION, BLINDING, CONTROL, PLACEBO, SAMPLE SIZE, INCLUSION AND EXCLUSION CRITERIA, END POINTS

CLINICAL RELEVANCE

26 GY IN 5 FRACTIONS (1 WEEK) IS NON-INFERIOR TO 40 GY IN 15 FRACTIONS (3 WEEKS) FOR LOCAL CONTROL, WITH SIMILAR LATE EFFECTS → PRACTICAL, PATIENT-FRIENDLY STANDARD FOR SUITABLE EARLY BREAST CANCER. 27 GY/5: HIGHER LATE NORMAL-TISSUE EFFECTS → GENERALLY AVOID



**STUDY DESIGN AND
METHODOLOGY**

•ENDPOINTS: WERE THEY PRIMARY VS SECONDARY, HARD VS SURROGATE?

**•INCLUSION/EXCLUSION CRITERIA: WHOM DOES THIS TRIAL
APPLY TO?**

•SAMPLE SIZE: WAS IT ADEQUATELY POWERED?

•CONTROL: PLACEBO, ACTIVE COMPARATOR, OR NO TREATMENT?

•BLINDING: SINGLE, DOUBLE, OR TRIPLE-BLIND?

RANDOMIZATION: HOW WERE PARTICIPANTS ASSIGNED?

TYPE OF STUDY: RCT, COHORT, CASE-CONTROL, ETC

TYPE OF STUDY

LEVEL OF EVIDENCE” :-IT IS GRADED, ITS SIGNIFICANCE ACROSS DIFFERENT STUDY TYPES IN CLINICAL TRIALS.

- **HIGHER LEVEL** = STRONGER CONFIDENCE THAT RESULTS REFLECT THE TRUE EFFECT.
- **LOWER LEVEL** = GREATER CHANCE OF BIAS OR CONFOUNDING

RANDOMIZED CONTROLLED TRIALS (LEVEL 2)

- REDUCES SELECTION BIAS.
- BEST FOR DETERMINING CAUSE-EFFECT IN INTERVENTIONS.
- LIMITATIONS: COSTLY, SOMETIMES ETHICALLY OR PRACTICALLY IMPOSSIBLE.

CASE-CONTROL STUDIES (LEVEL 4)

- COMPARE PATIENTS WITH A CONDITION (CASES) TO THOSE WITHOUT (CONTROLS).
- SIGNIFICANCE: FOR RARE DISEASES OR LONG LATENCY CONDITIONS, BUT RECALL AND SELECTION BIAS ARE MAJOR ISSUES.

CROSS-SECTIONAL STUDIES (LEVEL 5)

- SNAPSHOT IN TIME; MEASURE PREVALENCE.
- SIGNIFICANCE: GOOD FOR HYPOTHESIS GENERATION, POOR FOR CAUSALITY.

Meta
Analyses

Randomised
Controlled Trials

Cohort Studies

Case-Control Studies

Case-Series or Case-Reports

Editorials and Expert Opinion

SYSTEMATIC REVIEWS & META-ANALYSES (LEVEL 1)

- COMBINE DATA FROM MULTIPLE RCTS → INCREASES POWER & PRECISION.
- SIGNIFICANCE: GOLD STANDARD FOR CLINICAL GUIDELINES, MINIMIZES RANDOM ERROR, BUT DEPENDS ON QUALITY & HETEROGENEITY OF INCLUDED STUDIES.

COHORT STUDIES (LEVEL 3)

- FOLLOW EXPOSED VS UNEXPOSED GROUPS OVER TIME.
- SIGNIFICANCE: GOOD FOR PROGNOSIS, INCIDENCE, RISK FACTOR IDENTIFICATION. LESS STRONG FOR CAUSALITY DUE TO CONFOUNDING.

CASE REPORTS / EXPERT OPINION (LEVEL 5-6)

- DESCRIPTIVE; NO CONTROL GROUP.
- SIGNIFICANCE: USEFUL FOR RARE EVENTS, EARLY SIGNALS OF NEW CONDITIONS, BUT WEAKEST FOR DECISION-MAKING.

SIGNIFICANCE OF LEVEL OF EVIDENCE IN CLINICAL TRIAL

CLINICAL DECISION-MAKING: HELPS WEIGH BENEFITS VS RISKS CONFIDENTLY.

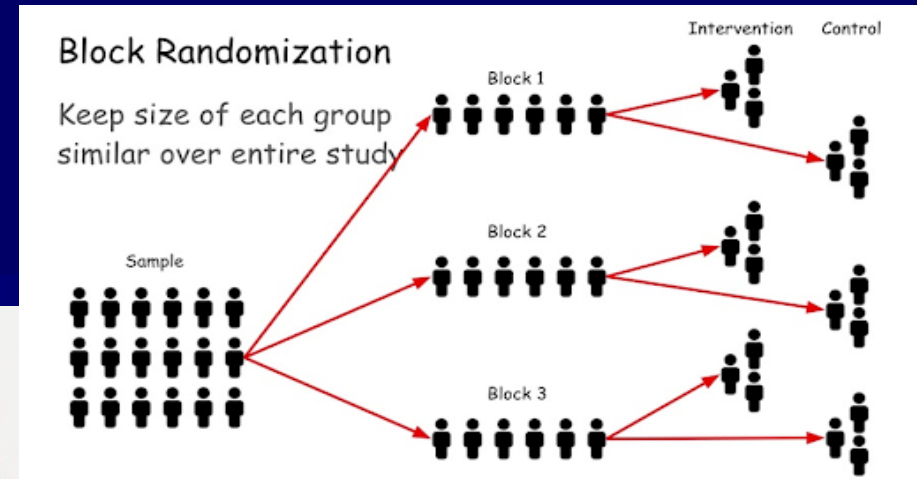
GUIDELINES: HIGHER-LEVEL EVIDENCE SHAPES STANDARD OF CARE

SIGNIFICANCE

RESOURCE ALLOCATION: FUNDS & RESEARCH PRIORITY GO TO QUESTIONS LACKING HIGH-LEVEL EVIDENCE.

REGULATORY APPROVAL: AGENCIES (FDA, EMA) RELY MORE ON LEVEL 1-2 DATA.

RANDOMIZATION



**SIMPLE
RANDOMIZATION**

LIKE COIN TOSS

**BLOCK
RANDOMIZATION**

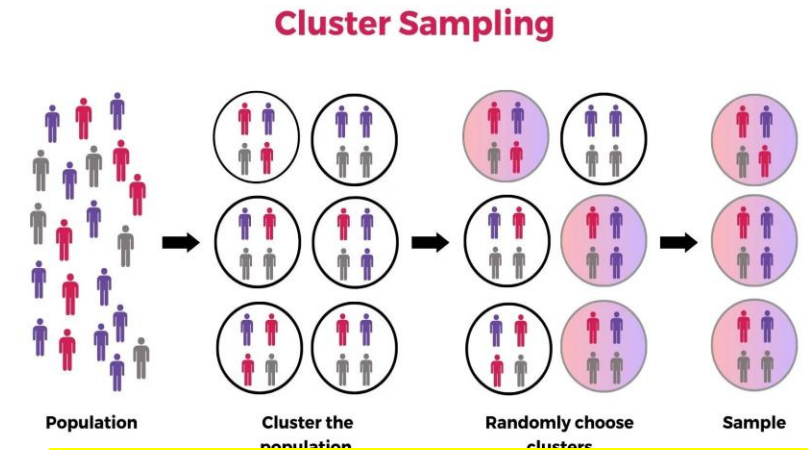
ENSURES EQUAL
SAMPLE SIZES

**STRATIFIED
RANDOMIZATION**

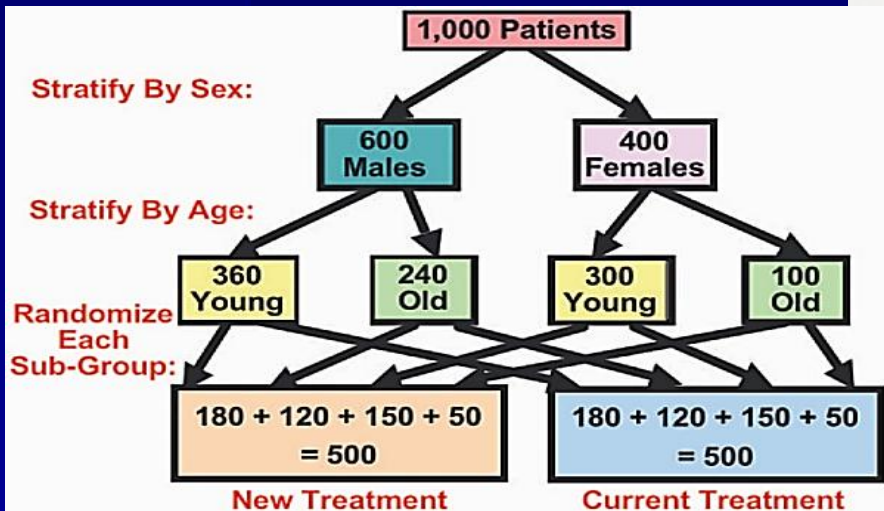
BALANCES
SPECIFIC VARIABLES

**CLUSTER
RANDOMIZATION**

RANDOMIZES
GROUPS



- Comparing hand hygiene programs → randomize hospitals.
- Comparing nutrition education → randomize schools.

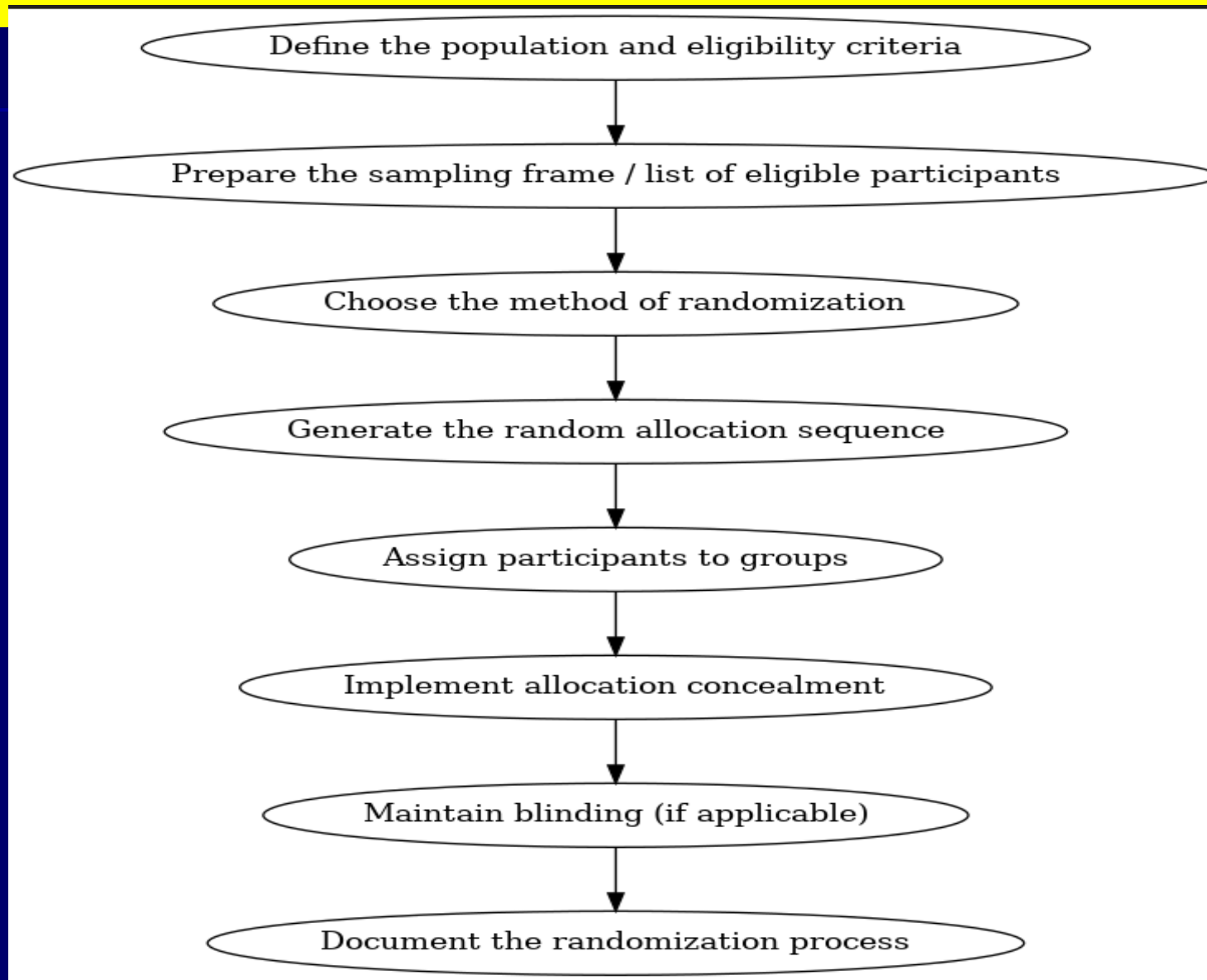


CLUSTERED VS BLOCK RANDOMIZATION

CLUSTER RANDOMIZATION	
Unit of Randomization	Groups (clusters) such as hospitals, schools, villages
Purpose	Prevent contamination when participants in the same group may influence each other
Example	Randomizing entire hospitals to intervention vs. control
Analysis Level	Usually analyzed at cluster level

BLOCK RANDOMIZATION	
Unit of Randomization	Individual participants, arranged in blocks
Example	Ensure equal numbers in each study arm at regular intervals
Analysis Level	Randomizing in blocks of 4 so each block has 2 intervention & 2 control
Analyzed at	Analyzed at individual level

PROCESS OF ASSIGNING PARTICIPANTS TO DIFFERENT GROUPS (E.G., INTERVENTION VS. CONTROL) BY CHANCE RATHER THAN BY CHOICE. Backbone of an RCT — without it, the trial risks bias, imbalance, and unreliable conclusions, SO RCTs are considered Level 2 evidence (and, when pooled in meta-analyses, Level 1).



BLINDING

METHOD TO PREVENT BIAS BY KEEPING CERTAIN MEMBERS UNAWARE OF WHICH INTERVENTION A PARTICIPANT RECEIVES.

SINGLE BLIND

PARTICIPANT :-BLIND

USED TO AVOID PLACEBO EFFECT

DOUBLE BLINDING

PARTICIPANT AND INVESTIGATORS ARE BLIND

GOLD STANDARD TO MINIMISE PERFORMANCE AND DETECTION BIAS

AVOID OBSERVOR BIAS

UNBIASED DATA ANALYSIS

IMPROVES INTERNAL VALIDITY OF DATA

TRIPLE BLINDING

PARTICIPANT, INVESTIGATOR AND ANALYSTS ARE BLIND

PREVENT ANALYTICAL BIAS

OPEN LEVEL TRIAL

NO BLINDING

DONE WHEN BLINDING IS IMPRACTICAL



STUDY DESIGN IN FAST FORWARD

Study Design

- **Type:** Phase III, multicenter, randomized, non-inferiority trial.
- **Randomization:** 1:1:1 into three arms (40 Gy/15F vs 27 Gy/5F vs 26 Gy/5F).
- **Sample size:** ~4096 women.
- **Follow-up:** Median 71 months (5.9 years).
- **Non-inferiority margin:** Hazard ratio upper CI ≤ 1.6 for local recurrence.

READ

ANALYZE THE RESULT

ABSTRACT

STUDY DESIGN

DISSECT

1. BASELINE CHARACTERISTIC
- 2. ABSOLUTE RISK VS RELATIVE RISK
- 3. HAZARD RATIOS, CONFIDENCE INTERVALS, P-VALUES
- 4. SUBGROUP ANALYSIS: EXPLORATORY OR PRE-SPECIFIED?
- 5. STATISTICAL SIGNIFICANCE \neq CLINICAL SIGNIFICANCE

ABSTRACT GIVES A SUMMARY:
QUESTION, METHODS, KEY
RESULTS, AND CONCLUSION

TYPE OF

STUDY, RANDOMIZATION, BLINDING,
CONTROL, PLACEBO, SAMPLE
SIZE, INCLUSION AND EXCLUSION
CRITERIA, END POINTS

CLINICAL RELEVANCE

**1. BASELINE
CHARACTERISTIC**

**2. ABSOLUTE
RISK VS
RELATIVE RISK**

**ANALYZE
THE
RESULT**

**3. HAZARD RATIOS,
CONFIDENCE
INTERVALS, P-
VALUES**

**4. SUBGROUP
ANALYSIS:
EXPLORATORY OR
PRE-SPECIFIED?**

**5. STATISTICAL
SIGNIFICANCE \neq
CLINICAL
SIGNIFICANCE**

Absolute Risk = $\frac{\text{Total number of people}}{\text{Number of people with the event}}$

ABSOLUTE RISK

Actual probability of an event in each group

GROUP	NUMBER OF PARTICIPANTS	HEART ATTACKS DURING STUDY
DRUG GROUP	1,000	20
PLACEBO GROUP	1,000	40

• ABSOLUTE RISK IN DRUG GROUP = $20 \div 1,000 = 2\%$
• ABSOLUTE RISK IN PLACEBO GROUP = $40 \div 1,000 = 4\%$

ABSOLUTE RISK REDUCTION

Difference in absolute risk between two groups

Absolute Risk Reduction (ARR) =
 $ARR = 4\% - 2\% = 2\%$

NUMBER NEEDED TO TREAT

Patients to treat to prevent one event

(NNT) = $1 \div ARR$ (in decimal form).
 $NNT = 1 \div 0.02 = 50 \rightarrow$ Treat 50 people to prevent 1 heart attack.

RELATIVE RISK

Risk in one group relative to another group

RELATIVE RISK (RR) COMPARES PROBABILITY OF AN EVENT IN TREATMENT GROUP TO CONTROL GROUP.

$$RR = \frac{\text{RISK IN CONTROL GROUP}}{\text{RISK IN TREATMENT GROUP}}$$

GROUP	HEART ATTACKS	PARTICIPANTS	RISK
DRUG GROUP	20	1,000	0.02 (2%)
PLACEBO GROUP	40	1,000	0.04 (4%)

$$\text{Relative risk:- } \frac{0.04}{0.02} = 0.5$$

•RELATIVE RISK REDUCTION (RRR) = 1 – RR.

INTERPRETATION

- RR = 1 → NO DIFFERENCE BETWEEN GROUPS.
- RR < 1 → TREATMENT REDUCES RISK (PROTECTIVE EFFECT).
RR = 0.5 → 50% LOWER RISK IN TREATMENT GROUP COMPARED TO CONTROL.
- RR > 1 → TREATMENT INCREASES RISK (HARMFUL EFFECT).

ABSOLUTE RISK

 Heart
attack

Drug group: 2%
Placebo group: 4%

2%

absolute risk

RELATIVE RISK

 Heart
attack

$$\frac{0.02}{0.04}$$

0.5

0,5

relative risk

Hazard Ratio (HR)

- **Definition:** A measure from survival analysis that compares the hazard (rate of an event occurring) in the treatment group vs. the control group over time.
- **Interpretation:**
 - **HR = 1** → No difference in hazard between groups.
 - **HR < 1** → Event is less likely in the treatment group (protective effect).
 - **HR > 1** → Event is more likely in the treatment group (harmful effect).
- **Example:**

If HR = 0.75, the treatment group has **25% lower risk** of the event at any given time compared to the control.
- **Hazard Ratio (HR = 0.70)**
- The treatment group has **30% lower hazard** (risk of the event occurring at any given time) compared to the control group.
- Since $HR < 1$ → **protective effect** of the treatment.

Confidence Interval (CI)

- **Definition:** A range of values that likely contains the true HR with a certain probability (usually 95%).
- **Interpretation:**
 - If the **95% CI does NOT include 1**, the result is statistically significant at $p < 0.05$.
 - **Narrow CI** → More precise estimate.
 - **Wide CI** → Less precise, often due to smaller sample size or fewer events.
- **Example:**
HR = 0.75 (95% CI: 0.60–0.95) → Since CI does not include 1, the result is statistically significant, and the effect is likely protective.
- **Confidence Interval (95% CI: 0.55–0.88)**
- The CI does **not include 1**, so the result is **statistically significant**.
- **Lower bound (0.55)** → could be as much as a 45% hazard reduction.
- **Upper bound (0.88)** → could be as little as a 12% hazard reduction.
- The interval is reasonably narrow → **precise estimate**.

- **Precision and Reliability**
- **Narrow CI (0.55–0.88)** → This suggests the estimate is relatively **precise**.
- Narrowness is influenced by:
 - **Sample size** (larger → narrower)
 - **Number of events** (more → narrower)
 - **Variability in data** (less variability → narrower)
- **Clinical and Statistical Significance**
- **Statistical:** CI does **not include 1**, so the effect is statistically significant at $p < 0.05$.
- **Clinical:** Both extremes of the CI (0.55 and 0.88) suggest a **clinically meaningful risk reduction**.
 - Worst-case (upper bound 0.88) → still ~12% hazard reduction.
 - Best-case (lower bound 0.55) → ~45% hazard reduction.
- You should always interpret HR **and** CI together:
 - If CI is **wide** and crosses 1 → the result may be unreliable or not significant.
 - If CI is **narrow** and does not cross 1 → the result is both **precise** and **statistically significant**.

p-value

- **Definition:** The probability of observing the result (or a more extreme one) if there were truly **no difference** between groups.
- **Interpretation:**
 - $p < 0.05$ → Statistically significant (less than 5% chance the result is due to random variation).
 - $p \geq 0.05$ → Not statistically significant.
- **Limitations:**
 - A small p-value doesn't mean the effect is clinically important—only that it's unlikely due to chance.
 - A large sample can make even tiny, clinically irrelevant effects statistically significant.

- **Look at HR** → Direction and magnitude of effect.
- **Check CI** → Precision of estimate & whether it includes 1.
- **Check p-value** → Statistical significance.
- **Example Interpretation:**
- HR = 0.70 (95% CI: 0.55–0.88), p = 0.002
→ Treatment reduces hazard by 30%, result is statistically significant, and the estimate is precise.

HAZARD RATIO

compares hazard
in treatment vs.
control group

$HR = 1 \rightarrow$ no difference

$HR < 1 \rightarrow$ event likely
in treatment group

$HR > 1 \rightarrow$ event more
likely in treatment group

EX = 0.75

treatment group has
25% lower risk

Example

$HR = 0.75$

treatment group has
25% lower risk

CONFIDENCE INTERVAL

range of values
likely containing
the true HR

if 95% CI does not incl. 1
 \rightarrow statistically significant

narrow CI \rightarrow more precise
wide CI \rightarrow less precise

Ex 0,60-0.95

P-VALUE

probability result
is due to chance

$p < 0.05 \rightarrow$ statistically
significant

$p \geq 0.05 \rightarrow$ not statistically
significant

Ex $p < 0.04$

BASELINE CHARACTERISTICS — WERE GROUPS COMPARABLE?

- **NUMBERS & BALANCE:** 4,096 participants randomized 1:1:1 (40 Gy/15f n=1361; 27 Gy/5f n=1367; 26 Gy/5f n=1368); treatment compliance ~99%. Demographic/clinical characteristics were **well balanced** per authors. [PubMed Central](#)
- **Key comparators (selected rows from Table 1):** median age 60–61 y across arms; breast-conserving surgery in ~93–94%; node-positive ~18–19% each; median tumor size 1.6 cm each; ER+/HER2- ~80–83% each; boost delivered in ~24–25% each. [PubMed Central](#)

ABSOLUTE RISK VS. RELATIVE RISK (LOCAL CONTROL AT 5 YEARS)

- **Ipsilateral breast tumor relapse (IBTR) — cumulative incidence at 5 y:**
 - 40 Gy/15f: **2.1%** (95% CI 1.4–3.1)
 - 27 Gy/5f: **1.7%** (1.2–2.6) → **ARD** vs 40 Gy = **-0.3%** (-1.0 to 0.9); **approx RR ≈ 0.81**
 - 26 Gy/5f: **1.4%** (0.9–2.2) → **ARD** vs 40 Gy = **-0.7%** (-1.3 to 0.3); **approx RR ≈ 0.67**. [PubMed Central](#)
(ARD = absolute risk difference; RR computed from reported cumulative incidences for reader intuition.)

HAZARD RATIOS, CONFIDENCE INTERVALS, P-VALUES (AS REPORTED)

- **Primary endpoint (IBTR, time-to-event):**
 - 27 Gy vs 40 Gy: **HR 0.86** (95% CI 0.51–1.44); **p=0.56** (superiority log-rank).
 - 26 Gy vs 40 Gy: **HR 0.67** (0.38–1.16); **p=0.15** (superiority log-rank).
 - **Non-inferiority test** (margin defined by critical HR 1.81): both five-fraction schedules met NI: **p=0.0022** (27 Gy) and **p=0.00019** (26 Gy). [PubMed Central](#)
- **Other disease endpoints (selected):**
 - **Locoregional relapse:** HR 0.80 (27 Gy) and 0.66 (26 Gy); p=0.33 and p=0.083, respectively.
 - **Distant relapse:** HR 1.16 (27 Gy), 1.27 (26 Gy); p=0.41, 0.17.
 - **All-cause mortality:** HR 1.12 (27 Gy), 0.96 (26 Gy); p=0.42, 0.78. [PubMed Central](#)

Normal tissue effects (safety), by Results analyses

- **Clinician-assessed, cross-section at 5 y (point prevalence):** 9.9% (40 Gy) vs **15.4% (27 Gy)** vs 11.9% (26 Gy) for “any

• **Cumulative incidence (Kaplan–Meier, time-to-first event, 1–5 y):** 26.8% (40 Gy) vs **35.1% (27 Gy)** vs 28.5% (26 Gy), reinforcing the above pattern (27 Gy higher; 26 Gy similar). [PubMed Central](#)

SUBGROUP ANALYSIS — EXPLORATORY OR PRE-SPECIFIED?

• **No formal subgroup analyses** of the primary endpoint were performed due to few events; only **descriptive tabulations** by age, grade, ER/HER2 are shown in the appendix. (Higher-grade tumors had more events, as expected.) These are **exploratory/descriptive**, not inferential. [PubMed Central](#)

• A **pre-planned nodal sub-study** (breast/chest wall ± axilla) compared 40 Gy vs 26 Gy and reported similar patient-reported arm/hand swelling at 24 months (10% vs 7% moderate/marked), supporting safety of 26 Gy when nodal fields are treated.

[PubMed](#)

STATISTICAL SIGNIFICANCE ≠ CLINICAL SIGNIFICANCE

• **Local control:** Although HRs trend <1 for 26 Gy, superiority **was not** demonstrated (p=0.15). The **absolute** 5-year difference in IBTR vs 40 Gy is **<1% (–0.7%)**, which is statistically non-inferior and **clinically small** in magnitude. [PubMed Central](#)

• **Toxicity:** The 27 Gy schedule shows a **statistically and clinically meaningful** increase in moderate/marked effects (OR 1.55 and ~+8 percentage-points in cumulative incidence 1–5 y), while **26 Gy shows no significant increase** — a clinically relevant distinction when selecting a 1-week regimen. [PubMedPubMed Central](#)

• **Survival/distant relapse:** No statistically significant differences; any numerical variations are **not** clinically actionable based on these data.

ALLOCATION
CONCEALMENT DONE

ANY LOSS TO
FOLLOW UP

INTENTION TO
TREAT DONE

VALIDITY

FUNDING
SOURCE/CONFLICT
OF INTEREST

OUTCOME
PRESPECIFIED

STRATEGIES TO MINIMIZE BIAS & IMPROVE VALIDITY

ADEQUATE SAMPLE SIZE → IMPROVES PRECISION

**RANDOMIZATION →
MINIMIZES SELECTION BIAS.**

STUDY GROUP

**Control groups →
Improves internal validity**



**BLINDING → REDUCES OBSERVER
AND MEASUREMENT BIAS**



**STANDARDIZED MEASUREMENT TOOLS → REDUCES
INFORMATION BIAS.**

**ADJUSTMENT FOR CONFOUNDERS → STATISTICAL CONTROL
(E.G., MULTIVARIATE REGRESSION).**

**ALLOCATION
CONCEALMENT?**
central remote
randomisation

ANY LOSS TO FOLLOW UP

lost to follow-up = 0 (27 Gy), 0 (26 Gy), 1 (40 Gy). (5-year visit forms available: 1231/1367, 1232/1368, 1218/1361; missing forms include deaths/withdrawals/non-returned forms.)

**VALIDITY
FASTFORWARD
TRIAL**

**INTENTION TO TREAT
DONE**

Primary analyses were ITT; because it's a non-inferiority trial, the primary endpoint was also tested per-protocol (pre-specified)

OUTCOME PRESPECIFIED

Primary endpoint = ipsilateral breast tumour relapse with a predefined non-inferiority margin ($\leq 1.6\%$ absolute excess; critical HR 1.81).

**FUNDING
SOURCE/CONFLICT OF
INTEREST**

Funded by NIHR Health Technology Assessment (09/01/47) Funder had no ROLE

Does the **study population match** your patients

Is the **intervention feasible** in your setting?

CLINICAL RELEVANCE, APPLY THE FINDINGS TO PRACTICE

Are the **benefits worth the risks/costs?**

Will it **change your practice or decision-making?**

PIBP

DOES THE STUDY POPULATION MATCH YOUR PATIENTS?

WHO WAS STUDIED? Adults with early invasive breast cancer (pT1–3, pN0–1, M0) after BCS or mastectomy, treated to whole breast or chest wall. Five-year outcomes showed 26 Gy/5F/1 week is non-inferior to 40 Gy/15F/3 weeks for local control, with similar normal-tissue effects (NTE); 27 Gy/5F had higher NTE.

UNDER-REPRESENTED GROUPS: Very young patients and immediate reconstructions were few; use judgement/audit if offering 26/5 in those scenarios.

DCIS: Not in the main RCT, but UK guidance now offers 26 Gy/5F for DCIS based on the totality of hypofractionation evidence.

IS THE INTERVENTION FEASIBLE IN YOUR SETTING?

PLANNING & DELIVERY: Standard tangents or IMRT/VMAT.. left-sided cases, DIBH is recommended. A sequential boost can follow 26/5 (either normofractionated or a short hypofractionated boost); SIB data with 5F is limited, so follow local policy.

THROUGHPUT & LOGISTICS: Moving from 15 to 5 visits markedly improves capacity and patient convenience;

UK services adopted 26/5 widely during COVID with good tolerability, and implementation series report low grade 3 acute skin toxicit

CLINICAL RELEVANCE, APPLY THE FINDINGS TO PRACTICE

EFFICACY & SAFETY:

IBTR at 5 y ~2.1% (40/15) vs 1.4% (26/5); NTE comparable for 26/5 and higher for 27/5—hence 26/5 is the preferred 1-week schedule.

[PUBMED](#)

PATIENT/COST IMPACT: Two-thirds fewer visits → lower indirect costs (travel, time off work) and frees linac time; health-system analyses highlight workflow efficiencies with 26/5. [PubMed](#)
[CentralScienceDirec](#)

EDGE CASES: With immediate reconstruction and some very young patients, data are limited—guidance advises offering 26/5 with caution and local audit. Are the benefits worth the risks/costs?

WILL IT CHANGE YOUR PRACTICE OR DECISION-MAKING?

YES—CONCRETELY, HERE'S HOW TO APPLY IT

Default whole-breast/chest wall after BCS or mastectomy (no immediate recon): Offer 26 Gy in 5F over 1 week as standard

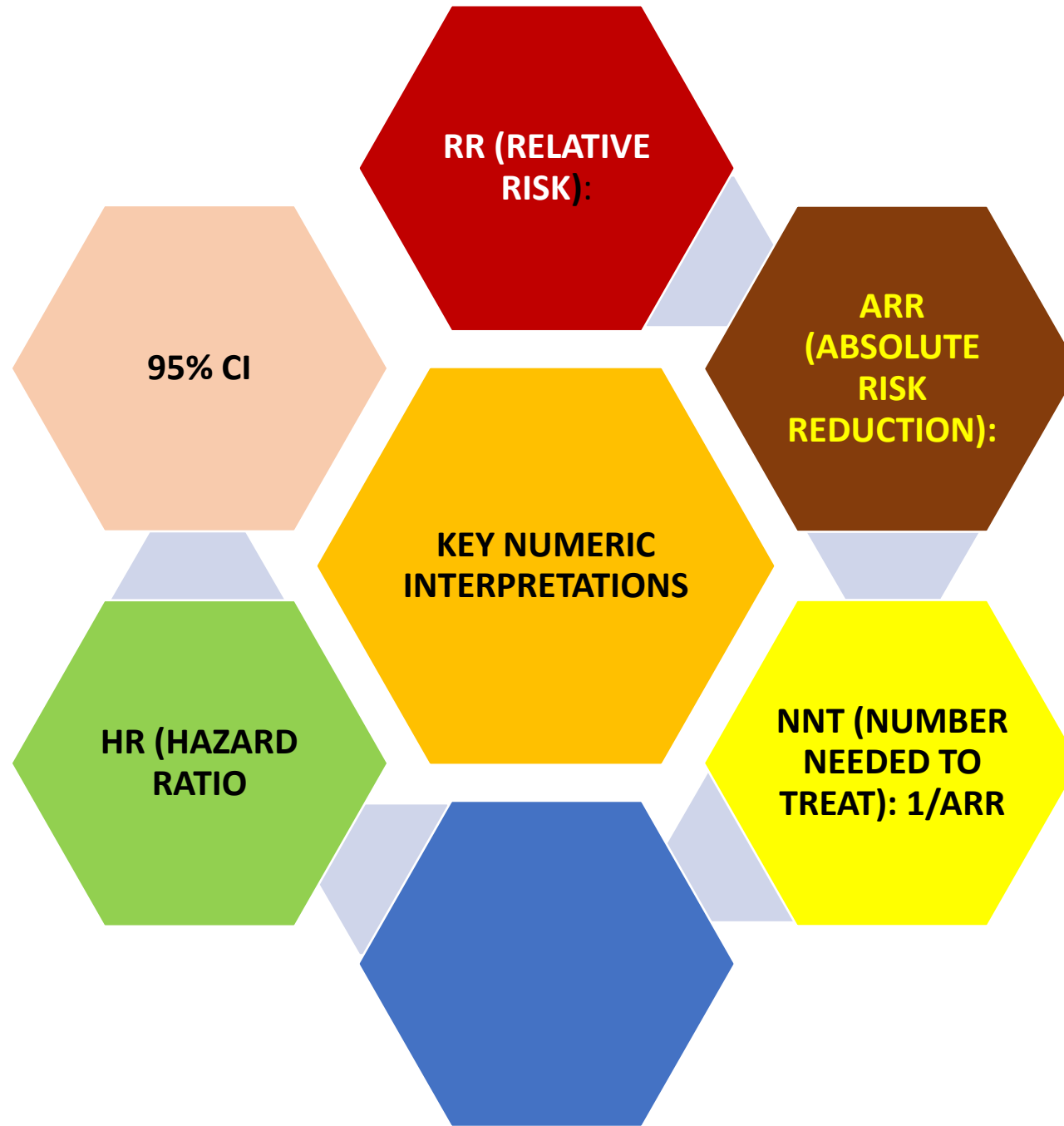
DCIS: Offer 26 Gy/5F (per UK guidance). [The Royal College of Radiologists](#)

Boost needed: Use sequential boost (normofractionated or short hypofractionated per local protocol); avoid untested SIB with 5F outside protocols. [The Royal College of Radiologists](#)

Regional nodes (RNI): [Guidelines \(2023\)](#): still recommend 40 Gy/15F for RNI. [The Royal College of Radiologists](#)

Emerging evidence: FAST-Forward nodal sub-study (n=469) shows reassuring 5-year patient-reported NTE with 26 Gy/5F axillary RT; consider within governance/audit or trials as your program gains experience. [PubMed](#)

Left-sided cases: Prioritize DIBH and modern planning to respect heart/LAD constraints.



KEY NUMERIC INTERPRETATIONS (PLACE BEFORE CONCLUSION)

Arm	5-yr IBTR	95% CI
40 Gy / 15F (control)	2.1%	1.4–3.1
27 Gy / 5F	1.7%	1.2–2.6
26 Gy / 5F	1.4%	0.9–2.2

Comparison (vs 40/15)	RR	ARR	NNT
26/5 vs 40/15	≈0.67	0.7%	≈143
27/5 vs 40/15	≈0.81	0.4%	≈250

- HR & 95% CI: Non-inferiority design; CIs for 26/5 compatible with non-inferiority (not designed to prove superiority).
- CI heuristic: For RR/HR, CI not crossing 1 → statistical significance; for NI, ensure CI lies within the prespecified NI margin.

Arm / Comparison	Moderate/Marked NTE at 5 y	OR vs 40/15	95% CI	NNH (from ARI)
40/15 (reference)	9.9%	—	—	—
27/5 vs 40/15	15.4%	1.55	1.32–1.83	≈18 (ARI 5.5%)
26/5 vs 40/15	11.9%	1.12	0.94–1.34	≈50 (ARI 2.0%)

NUMERICAL INTERPRETATION KEY NUMBERS & PRACTICAL TAKE-HOMES

- Primary endpoint (5-yr IBTR): ~2.1% (40/15) vs ~1.4% (26/5) — met non-inferiority.
- Late normal-tissue effects: 26/5 \approx 40/15; 27/5 higher NTE \rightarrow 26/5 preferred.
- Population: early breast cancer post-BCS or mastectomy; pragmatic, multicentre.
- Implementation: 5-fraction schedule reduces visits by ~67% (15 \rightarrow 5).
- Use judgement for very young patients and immediate reconstructions (limited numbers).

Refs: Brunt et al., Lancet 2020 (FAST-Forward); HTA Monograph 2020; UK RCR Dose-Fractionation Guidance.

CONCLUSION: CAUTION WITH HYPE



DO NOT RELY ON
AUTHOR'S CONCLUSION

DO NOT RELY ON MEDIAS
HEADLINES

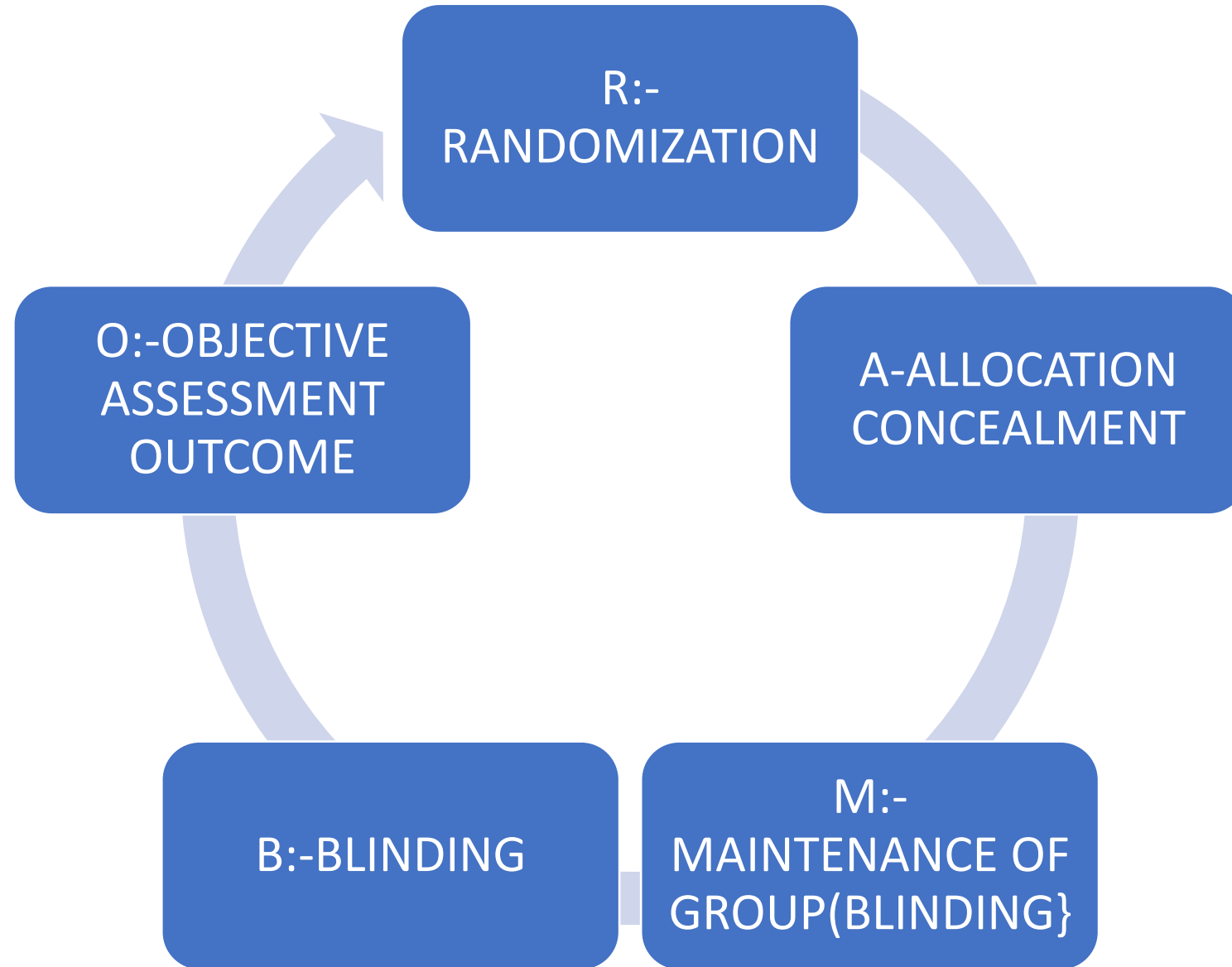
DO NOT RELY ON INDUSTRY-
FUNDED TRIAL

ALWAYS BALANCE EVIDENCE QUALITY WITH CLINICAL JUDGMENT.

CONCLUSION: CAUTION WITH HYPE — JUSTIFIED WITH FAST-FORWARD

- **NON-INFERIORITY ≠ SUPERIORITY**: designed to show 26 Gy/5F **IS NOT WORSE** than 40/15 for 5-yr IBTR; **DO NOT OVERSELL IT AS “BETTER.”**
- **SMALL ABSOLUTE DIFFERENCES**: **Event rates** were low; ARR for IBTR with 26/5 vs 40/15 is ~**0.7%** (NNT ≈ 143). Emphasize magnitude, not just statistical framing.
- **HARMS NUANCE**: 27/5 increased moderate/marked normal-tissue effects; 26/5 did not. Avoid generalizing to “any” 5-fraction schedule—prefer 26/5.
- **FOLLOW-UP HORIZON**: Median ~6 years. Some late effects (fibrosis, rib fracture, cardiac, second cancers) may emerge beyond 10 years—continue surveillance.
- **SUBGROUPS UNDER-REPRESENTED**: Very young patients, immediate reconstructions, and comprehensive RNI had limited data. Use governance/audit when extrapolating.
- **IMPLEMENTATION MATTERS**: Use DIBH for left-sided cases, adhere to OAR constraints, watch hotspots/homogeneity; avoid SIB with 5F outside protocols.
- **SYSTEM CONTEXT**: 5 visits improve throughput/costs, but operational gains must not override patient-specific factors and shared decision-making.
- **FUNDING/REPORTING**: Publicly funded and well-reported lowers bias risk, but still balance trial evidence with clinical judgment and patient values.
- **PRACTICE STANCE**: Default to 26 Gy/5F for suitable early cases; keep 40/15 for RNI until evidence matures; document informed consent and plan quality checks.

TIP: Mnemonic to Remember Appraisal Steps — “R.A.M.B.O



FINAL STEP: INTEGRATE INTO PRACTICE

**DISCUSS WITH
TEAM/PATIENT**

**ALIGN WITH
GUIDELINES OR
PROTOCOLS. CONSIDER
COST-EFFECTIVENESS**

**IF STRONG
EVIDENCE**

**CONSIDER COST
EFFECTIVENESS**

PATIENT PREFERENCE

