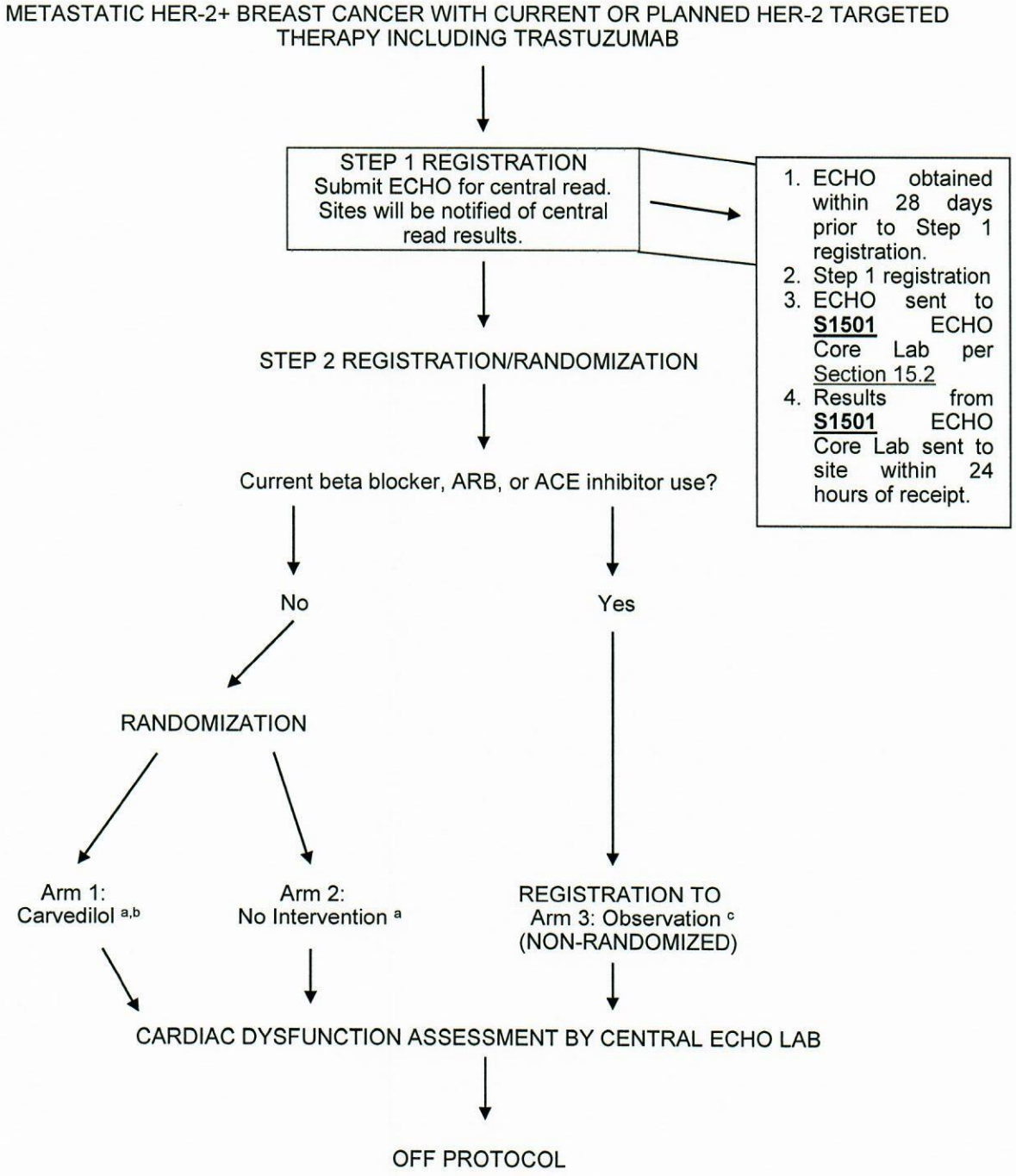
SCHEMA



Footnote[a] HER-2 targeted therapy continuation/discontinuation at the discretion of treating physician.

Footnote[b] For patients on Arm 1, carvedilol is reimbursed by the study while the patient is on study for up to 108 weeks from randomization. Upon removal from study, non-reimbursed carvedilol continuation is at the discretion of the treating physician.

Footnote[c] Patients already on beta blocker, ARB or ACE inhibitors.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or cancercontrolquestion@crab.org prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 21 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 STEP 1 REGISTRATION

a. Disease Related Criteria

_____ 1. Patients must have metastatic breast cancer and be initiating within 7 days of Step 1 Registration or continuing trastuzumab–based HER-2 targeted therapy without concurrent anthracyclines in first or second line setting. Patients may have brain metastasis. There is no limit for number of doses of HER-2 targeted therapy prior to registration. Examples of eligible HER-2 targeted therapy:

- Trastuzumab
- Trastuzumab + chemotherapy or hormonal therapy
- Trastuzumab + other HER-2 targeted agent with or without chemotherapy (such as pertuzumab)
- Ado-trastuzumab (Kadcyla®)

NOTE: Patients on lapatinib without trastuzumab are not eligible. Planned treatment with concurrent HER-2 targeted therapy and anthracyclines is not permitted.

b. Prior/Concurrent Therapy Criteria

_____ 1. Patients must be at increased risk for cardiotoxicity defined by at least one of the following:

a. Previous anthracycline exposure

OR

b. 1 or more of the following risk factors for heart disease:
- LVEF 50-54% by local ECHO read
- Age ≥ 65
- BMI ≥ 30 kg/m^2
- Current or prior anti-hypertensive therapy
- Diagnosis of coronary artery disease (CAD)
- Diabetes Mellitus
- Atrial fibrillation/flutter

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 STEP 1 – REGISTRATION (contd.)

_____ 2. Patients must not have taken within 21 days prior to Step 1 Registration, be currently taking at the time of Step 1 Registration, or planning to take once registered to Step 1 a beta blocker, ARB, or ACE inhibitor in order to be randomized (Arms 1 and 2).

Patients currently taking a beta blocker, ARB, or ACE inhibitor at the time of Step 1 Registration are eligible to register for the non-randomized observational cohort (Arm 3).

_____ 3. Patients must not be currently taking or planning to take during study treatment the following medications:

- B2 agonists
- Bosutinib
- Ceritinib
- Floctafenine
- Methacholine
- Pazopanib
- Rivastigmine
- Vincristine
- Silodosin

c. Clinical/Laboratory Criteria

_____ 1. Patients must have a Zubrod Performance Status of 0-2. (see Section 10.5)

_____ 2. Patients must be ≥ 18 years of age.

_____ 3. Patients must have a complete physical examination and medical history within 28 days prior to registration.

_____ 4. Patients must have LVEF ≥ 50% by 2-D echocardiogram within 28 days prior to registration. The echocardiogram must be obtained from a **S1501** validated ECHO lab (see list of site "Validated ECHO Labs" on the **S1501** protocol abstract page at www.swog.org) and submitted for central review by the **S1501** ECHO Core Lab (see Section 15.2). ECHO should not be submitted for central read until patient has been otherwise deemed eligible.

_____ 5. Patients must have adequate hepatic function as evidenced by all of the following within 28 days prior to registration: serum bilirubin < 3.0 x institutional upper limit of normal (IULN), SGOT/AST and SGPT/ALT < 5.0 x IULN.

_____ 6. Patients must have electrocardiogram with QTc with correction within 28 days prior to registration.

_____ 7. Patients must have a systolic blood pressure ≥ 80 mm Hg within 14 days prior to registration.

_____ 8. Patients must not be dialysis dependent.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 STEP 1 – REGISTRATION (contd.)

_____ 9. Patients must be able to swallow tablets.

_____ 10. Patients must not have uncontrolled asthma.

_____ 11. Patients must not co-enroll on other treatment trials.

_____ 12. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, prostate cancer on active surveillance, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

_____ 13. Patients must not be pregnant or nursing due to potential fetal or nursing infant harm. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

d. Specimen Submission Criteria

_____ 1. Patients must be willing to submit blood specimens as outlined in Section 15.1.

_____ 2. Sites must seek additional patient consent for the future use of specimens as described in Section 15.0.

e. Regulatory Criteria

_____ 1. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ 2. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.2 STEP 2 REGISTRATION (Randomization)

An e-mail notification from the **S1501** ECHO Core Lab should be received by the site within 24 hours of submission of the baseline ECHO (unless submitted on a Friday, Saturday, or accepted holiday).

The following additional criteria must be met in order for a patient to be considered eligible for registration to the randomized trial. Any potential eligibility issues should be addressed to the Data Operations Center at cancercontrolquestion@crab.org prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.2 STEP 2 REGISTRATION (Randomization) (contd.)

_____ a. **Patients must not be registered to Step 2 until receiving confirmation from the ECHO Core Lab that the patient's LVEF by echocardiogram was ≥ 50% by central review. Patients must be registered within 5 calendar days of receiving the e-mail notification.**

_____ b. Site must verify that there is no known change in the Step 1 eligibility since initial registration.