A pragmatic randomised, multicentre trial evaluating the dose timing (morning vs evening) of endocrine therapy and its effects on tolerability and compliance (REaCT-CHRONO Study).

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PROTOCOL SIGNATURE PAGE

My signature below confirms that I have reviewed and approved this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and all applicable local regulations

_____

Qualified Investigator (Please Print)

_____

Qualified Investigator Signature

_____

Date

Table of Contents

1 BACKGROUND

Endocrine therapy in breast cancer

Endocrine therapy is an established treatment for hormone receptor-positive breast cancer [1–3]. Endocrine therapy can cause significant side effects with deterioration in quality of life[4]. Tamoxifen and aromatase inhibitors (e.g. letrozole, anastrozole and exemestane) share common side effects such as hot flashes, arthralgia/joint stiffness, insomnia, weight gain, mood changes, gastrointestinal symptoms, and skin and vaginal dryness. In addition, while tamoxifen carries a higher risk of vaginal bleeding or discharge, thromboembolic events and uterine cancer, the aromatase inhibitors are associated with an increased risk of cardiovascular events, osteoporosis and bone fractures[5–7].

Non-persistance or non-compliance to endocrine therapy

The side effects of all forms of endocrine therapy are well recognised and can lead to treatment non-persistance or non-compliance. Compliance is defined as the degree or extent of conformity to the recommended administration by the provider, whereas persistence refers to the act of continuing treatment for a certain prescribed duration[8]. A systematic review of adjuvant endocrine treatment found that 41 to 72% of patients did not take the correct dosage at the prescribed frequency and 31 to 73% discontinue endocrine therapy[9]. Treatment adherence is especially important in breast cancer, as early cessation or reduced compliance to hormonal therapy are associated with reduced disease-free survival and increased mortality[10,11]. In order to maximize adherence, strategies have been used to mitigate these side effects. Regarding the hot flashes,

patients may benefit from lifestyle changes such as exercising and avoiding caffeine, alcohol as well as smoking[12,13]. Many nonhormonal pharmacotherapies have been used to try controlling vasomotor symptoms including selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors antidepressants, gabapentin and oxybutynin[13]. Most recently the Oncology Nursing Society published guidelines for cancer related hot flashes suggesting the use of sertraline, fluoxetine, escitalopram, duloxetine or clonidine. However, these pharmacologic strategies to control endocrine therapy side effects present their own array of potential side effects and often not well tolerated themselves[14].

Chronotherapy

Chronotherapy, also called chronotherapeutics, is defined as the administration of a medication in coordination with the circadian rhythm in order to minimize side effects and yield a greater efficacy[15]. While this concept is based on a strong mechanistic foundation involving xenobiotic metabolism and detoxification of drugs, only a few clinical trials, mainly for neurologic, behavioral and psychiatric conditions, factored in circadian timing[15]. Recently, a study demonstrated that the time of day at which antihypertensives are taken can impact their effectiveness[16]. In breast cancer, one randomized trial evaluating the optimal time for administering vinorelbine showed a non-statistical benefit for the incidence of grade 3-4 neutropenia when administered at 21:00 and grade 3-4 gastrointestinal toxicity when administered at 10:30[17]. Furthermore, there is some evidence suggesting that the adherence to drugs might be greater in the morning as compared to the evening[18]. Many online forums exist with breast cancer patients seeking insight on the time of day (i.e. morning vs evening) to take their endocrine therapy[19]. In

our practice, we often see doctors and nurses using a trial and error method to help patients determine the best time of day at which to take their endocrine therapy to try reducing these side effects, with anecdotal success. Even though this clinical practice is not evidence-based, there is increasing molecular evidence suggesting an interplay between circulating estradiol and expression of circadian clock genes that may support this practice[20].

Evidence from a recent systematic review

Our team recently conducted a systematic review to assess the evidence currently available regarding the circadian administration of endocrine therapy in terms of side effects, quality of life and disease-free survival in breast cancer patients. Ovid Medline, EMBASE, and the Cochrane Central Register of Controlled Trials were searched from 1947 to August 2020 for relevant randomized control trials or prospective cohort studies and off 361 unique citations identified, 0 studies met eligibility criteria.

Ongoing clinical trials

A search of the ClinicalTrials.gov database to identify all active registered trials looking at the best “time-of-day” administration of endocrine therapy was done on December 18, 2020. No registered studies on this specific question were found.

Clinical trial rationale

Although optimal time-finding trials have been conducted in other medical fields, none have been undertaken for hormonal therapy in breast cancer[15,20]. Patients and clinicians are relying on a trial and error approach to determine the best time of treatment with the goal of reducing side effects and improving QoL and adherence. However, this practice is neither evidence-based nor standard of care. Therefore, conducting the **world's first prospective randomized clinical trial** to evaluate the dose timing (morning versus evening) of endocrine therapy and its effects on tolerability and adherence is warranted and needed.

Clinical trial significance

Nonadherence and discontinuation of endocrine therapy has been an important clinical issue given its high prevalence and its negative impact on breast cancer mortality[11,21]. New non-pharmacological interventions to improve adherence and side effect profile of endocrine therapy are critically needed[11]. Changing the time of the day at which a medication is taken is a new, simple, easy intervention that does not generate additional costs.

From a patient perspective, finding a new strategy to reduce side effects associated with endocrine therapy will improve the quality of life of thousands of Canadian women with breast cancer and will help increase their compliance to endocrine therapy. Optimizing adherence to endocrine therapy by changing the time of the day at which it is taken will have a positive impact on breast cancer outcomes. Furthermore, this will reduce indirect

cost related to breast cancer recurrence and the use of pharmacological interventions to reduce side effects.

1.1 Pragmatic trials

Since 2014 the Rethinking Clinical Trials (REaCT) has been operating across Canada with the specific aim of performing pragmatic trials when physicians do not know what the "best" treatment for patients is, and genuine uncertainty ("clinical equipoise") exists. Currently the choice between taking endocrine therapy in the morning or evening depends more on choosing between different "standards" in their personal practice, using idiosyncratic decision-making processes, without the physician or the patient relying on an evidence-based option. Determining the optimal treatment timing remains an important medical issue for both patients and physicians.

This study will use robust methodology to allow comparisons of established standard of care treatment using the "integrated consent model" as part of a pragmatic clinical trial[22]. By integrating medical and clinical practices, physicians will be able to inform their patients about the RCT, through a typical conversation between the physician and patient, with oral informed consent. This clinical interaction would then be documented in the consult note, as ordinarily done in practice.

Pragmatic clinical trials are being given increased importance, as they commonly consist of comparative effectiveness research, thus comparing the safety and effectiveness of

diagnostic, therapeutic or delivery systems. Additionally, these studies have not only the ability to leverage patient data from electronic health records to increase sample size of trials at much lower costs, but also enabling major national and international initiatives to generate the data needed to improve care[22]. As such, the Integrated Consent Model is being increasingly used internationally to improve patient care[22,23]. In fact, The Ottawa Hospital Cancer Centre is leading this program with over 3000 patients already enrolled on REACT trials at 15 Canadian Cancer Centres. These studies have shown excellent patient feedback with 97% of patients rating being 'completely satisfied' with the REaCT process.

Thus, we propose to perform a pragmatic, multicentre, open-label, randomized clinical trial to establish the optimal timing (morning vs evening) of administering endocrine therapy based on side effects and benefits in early stage breast cancer patients.

1.2 Central Hypothesis or Research Question

Hypothesis: We hypothesize that the dose timing (morning vs evening) of endocrine therapy will impact side effects and benefits as assessed using the validated Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES)[24,25].

2 OUTCOMES

2.1 Primary Outcome

- Endocrine toxicity and tolerability measured by the change in total FACT-ES score (a validated subscale of the FACIT measurement system) from baseline to 12 weeks following the beginning of endocrine therapy

2.2 Secondary Outcomes

- Endocrine toxicity and tolerability measured by the change in total score and individual items of FACT-ES from baseline to 4, 8, 12 and 52 weeks following the beginning of endocrine therapy
- Quality of life measured by the change in the total score and individual subscales of the validated Functional Assessment of Cancer Therapy for patients with a Breast cancer (FACT-B) questionnaire from baseline to 4, 8, 12 and 52 weeks following the beginning of endocrine therapy
- Rates of discontinuation, interruption and non-compliance (defined as patient taking less than 80% of the prescribed endocrine therapy) with initially prescribed endocrine therapy
- Cost-effectiveness: incremental cost-effectiveness ratios (cost per one quality-adjusted life year (QALY) gained

2.3 Exploratory analyses

- Comparing rates of non-persistance or non-compliance with patient age, tumour stage, chemotherapy use, type of endocrine therapy

2.4 Interim analysis / feasibility

An interim analysis will be performed after the first year of study initiation, focusing on recruitment and safety aspects only. The study will be stopped if recruitment is <80 patients (~40% of total target) after one year or if considerable unanticipated safety issues arise.

3 STUDY DESIGN

The study schema is shown in Figure 1. Eligible patients with hormone receptor positive breast cancer who will receive adjuvant endocrine therapy will be eligible for this study. Patients will be consented either by their treating medical oncologist or a member of their circle of care. Consenting patients will be randomized to one of two arms:

Arm A: Morning administration of endocrine therapy defined as, within one hour of the patient wake up time.

or

Arm B: Evening administration of endocrine therapy defined as, within one hour of the patient bed time.

There will be no study mandated change in either the type of endocrine therapy. Endocrine therapy can be started either before, prior or after radiation therapy prescribed, as per patients' choice.

Patients will be approached by their medical oncologists during routine clinic visits. In order to ensure trial findings are applicable to the broadest population possible, eligibility

criteria will be pragmatic. Patients will be assessed either as per their usual clinic visits, or as the study does not involve additional clinic visits, study questionnaires will be completed via electronic link sent via email. The questionnaires will be built into the electronic database developed by the Ottawa Methods Centre and patients will receive a secure electronic link to complete the questionnaires at the required study timepoints. If patients do not have access to a computer/internet, they can request to receive paper copies in the clinic or by mail.

Outcomes will be measured at:

- Baseline (prior to start endocrine therapy)
- 4 weeks (± 1 week) after the start of endocrine therapy
- 8 weeks (± 1 week) after the start of endocrine therapy
- 12 weeks (± 2 week) after the start of endocrine therapy
- 52 weeks (± 2 week) after the start of endocrine therapy

The study calendar is shown in Table 1.

3.1 Consent Process

Potential study participants will be approached by their medical oncologist at the time of their routine clinic visit during the aforementioned timeline. The physician will give the patient an Information Sheet that briefly outlines the study and answer any questions. Patients will be asked to provide oral consent to be randomized to one of the two pre-specified treatment arms**.** This integrated consent model is akin to a typical conversation between the physician and patient and the interaction is documented in the patient's

medical record. Written informed consent will not be sought as the integrated consent model is ethically acceptable as the only prominent change to the standard of care treatment is the randomization process and there is no evidence-based standard of care for dose timing of endocrine therapy.

4 ELIGIBILITY

4.1 Inclusion Criteria

- Patients with an early stage or locally advanced hormonal receptor positive breast cancer
- Plan to receive endocrine therapy
- Age ≥18 years
- Able to provide oral consent
- Willing and able to complete questionnaires as per study protocol

4.2 Exclusion Criteria

- Metastatic cancer
- Previous endocrine therapy for breast cancer
- Plan to receive adjuvant abemaciclib

5 STATISTICAL ANALYSIS AND SAMPLE SIZE CALCULATION

5.1 Sample size

Our primary outcome is the change in total FACT-ES score from baseline to 12 weeks following the beginning of endocrine therapy.

Based on Fallowfield et al., a clinically meaningful effect would be observed if the change exceeded 0.5 of the standard deviation at baseline and the standard deviation at baseline is approximately 8.5[25]. Therefore a 'clinically meaningful change' from baseline to 12 weeks would be a change of 4.25 or greater. It is also assumed that 40% of patients will experience a clinically meaningful change, and prescribing the time of day for administration of treatment would be important if there was an actual difference in clinically meaningful change rates of 20% or more (i.e. 40% with a clinically meaningful change in one arm and 60% in the other). Therefore, based on these assumptions and using a two-sided, alpha=0.05 Fisher's exact test, we would need 214 total patients to achieve 80% statistical power. To account for potential loss to follow-up, and to account for stratification factors, the target sample size will be inflated by 10% to a total of 235.

5.2 Analysis Methods

Descriptive analysis: Baseline characteristics will be presented with means (continuous measures) or proportions (categorical or ordinal data) with 95% confidence intervals.

Intention-to-treat analysis: The primary analysis will be based on the intent-to-treat principle, thus, all participants who are randomized will be included in the final study analysis. The last observation carried forward method will be used to impute results for any patient who is lost to follow-up, or who does not have a FACT-ES score measured at the 12 week time point. This is a conservative approach to imputation, as it will likely result in smaller differences between groups than would actually be present (if there is an actual difference), under the assumption that increased effects will occur over time up to week 12. In addition, a per protocol analysis of the primary outcome measure will be conducted,

which will include only those patients who follow the intervention as prescribed in the protocol, and who complete both the baseline and 12 week FACT-ES score.

Analysis of primary and secondary outcomes: Dichotomous outcomes will be summarized according to proportions and 95% confidence intervals. Continuous outcomes will be summarized according to means and standard deviations or medians and interquartile ranges as appropriate. The primary analysis will be based on a logistic regression analysis with adjustment for stratification factors. Additional logistic and linear regression analyses will be performed with adjustment for stratum. Univariable comparisons between the intervention and control groups will be examined using a Chi-Squared test for dichotomous events, and a student's t-test for continuous measures. Non-parametric methods may be used in lieu of these tests as appropriate. All analyses will be supplemented with 95% confidence intervals where relevant.

Health economic evaluation: We will perform a cost utility analysis alongside this pragmatic randomized controlled trial. Resource use and health utility values will be measured from the trial at the baseline and follow up interviews. We will derive health utility values from the European Quality of Life-5 Dimensions 5-level (EQ-5D-5L) questionnaire. We will develop a Markov model that represents lifetime experience of a patient cohort following her treatment option to predict the long-term prognosis of patients. The model will consist of multiple distinct states, representing breast cancer progression and relevant adverse events. It will also have the capacity to capture medication adherence. We will derive input parameters required for the model from the concurrent trial and the published literature. The results will be presented as incremental cost per quality-adjusted life year (QALY) gained and incremental cost per one endocrine toxicity

case averted. Both costs and outcome will be discounted at 1.5% annually. A series of sensitivity analysis will be undertaken to examine the effect of conducting a complete case only analysis and of varying input parameters. Parameter uncertainty will be assessed using Monte Carlo simulations with 10,000 simulations. The results of the simulations will be shown as effectiveness acceptability curves (CEACs), which represent the probability of a treatment being cost-effective to a range of potential threshold values that the health system may be willing to pay for an additional unit of effect. All analysis will be conducted using Microsoft Excel.

Compliance and loss to follow-up: Supportive analyses will be performed to better understand the impact of non-compliance, loss to follow-up and protocol violations. The primary analysis is clearly defined, and other analyses will be performed understanding the supportive and secondary nature of these results. Interpretation of results will be performed, clearly acknowledging the a priori defined primary analysis.

5.3 Randomization and Stratification

Eligible and consented patients will be randomized using a permuted block design developed by the Ottawa Methods Centre to receive either one of the two study arms (1:1). The variable block sizes will be randomly selected between sizes of 4 and 6. Subjects will be stratified based on: study site, tamoxifen (yes/no), and chemotherapy (yes/no). The patient will be randomized through a secure web-based randomization system on the physician's clinic desktop or mobile device or through the designated study CRA. The randomization system also confirms the study eligibility criteria prior to randomization. The study does not involve changing the standard of care patients receive.

The study co-investigators (i.e. study qualified physicians) will ensure verbal consent and eligibility review has taken place prior to randomization. For all patients, the primary oncologist will dictate in the patient's electronic medical record that the consent process has taken place.

5.4 Blinding

Patients and investigators will not be blinded to treatment allocation as the study is randomizing treatment schedule only. This is in keeping with a pragmatic trial design

6. TIMELINE AND FOLLOW-UP

We would anticipate that the study will take two years for accrual and 1 year for completion of follow-up on the quality of life primary study endpoint. Therefore, we would anticipate that the study runs for 2.5 years.

7. DATA COLLECTION

Once the patient has been randomized, the study CRA will collect participant information on patient demographics (e.g. age), tumour characteristics (e.g. stage), surgery type, chemotherapy use, radiotherapy use and endocrine therapy type. From a study standpoint only the CRA will access this information. Data not available at the time of visit will be collected from the dictated physician note. CRAs will enter data into the electronic database developed by the Ottawa Methods Centre within the timeframes agreed in the site agreement.

The physician will document any study related events either in his dictated physician note and will complete a Health Care Provider Questionnaire at the 12 week clinic visit and at 52 weeks (end of study). This questionnaire will collect study related events including:

compliance to dose timing (date at which patient decided to change dose time and reasons), discontinuation of endocrine therapy (date and reasons), switch from an endocrine therapy type to another one (date and type and reasons). To reflect real-world practice, no additional clinic visit will be required, but participants will be contacted by a CRA or a health care provider at 12 weeks and 52 weeks to collect compliance information. In addition, treating physicians are encouraged to email the CRA if at any time a significant event (i.e. hospitalization, recurrence or death) occurs.

Participant data to be collected over the treatment period:

- Treatment assignment
- Treatment received
- FACT-ES questionnaire for assessing endocrine therapy symptoms and FACT-B questionnaire for assessing quality of life. Because the first portion of the FACT-ES and FACT-B questionnaires are the same, we will only have study participants complete the duplicate sections once at each time point (combined into FACT-B and ES questionnaire)
- Follow up questions about compliance to endocrine therapy, compliance to dose timing, dose interruptions, discontinuation and reasons for discontinuation, switch from an endocrine therapy type to another one
- EQ-5D-5L questionnaire for assessing health utility values to facilitate a cost-utility analysis
- Timing preference questionnaire will be collected from the participant at the beginning and end of the study

If the patient is randomized and either the patient or physician refuses the randomization selection, reasons for this will be recorded. If physicians choose to break the protocol, they must inform the patient as to why the allocated selection should not be used from the randomization process. We will monitor the charts to ensure that this reason has been recorded.

Participating sites will be responsible for maintaining a master list of eligible, enrolled patients, including first name, last name, date of birth (month and year only). This list will be generated, password-protected and maintained by the research coordinator, and stored on the secure hospital network at each site.

8. RISKS

There are no incremental risks associated with this study as both arms are standard of care treatments.

9. PREMATURE WITHDRAWAL

Participants have the right to withdraw from the study treatment at any time for any reason.

Investigator has the right and obligation to withdraw subjects from the study treatment in the event of:

- Intercurrent illnesses which would, in the judgment of the investigator, affect assessment of clinical status to a significant degree, and require discontinuation of protocol therapy

- Any toxicity that would produce further harm if subject continued on the protocol
- Request by the participant or of their legally authorized representative (consent withdrawal)
- Non-compliance to the study protocol or logistic consideration
- Participant is lost to follow-up

The reason for withdrawal will be collected on the End of Study case report form so that it can be presented in the CONSORT diagram.

10. MONITORING

This study will be conducted according to the International Conference on Harmonisation Good Clinical Practice Guidelines. Routine quality assurance and monitoring will be completed by the REaCT study team to ensure that the study is being run according to the protocol at each participating site. This monitoring will include:

- random spot checks on inclusion and exclusion criteria to confirm that only eligible patients are participating in the trial
- routine evaluation of source data to ensure accuracy
- evaluation of the data from the first participant and corresponding source documents from each site (de-identified and uploaded to the REaCT SharePoint site) to ensure that they are being completed according to the protocol.

The investigator(s)/institutions(s) will permit trial-related monitoring, audits, REB review and regulatory inspection(s), providing direct access to source data/documents as required.

11. FIGURES

Figure 1 Study schema

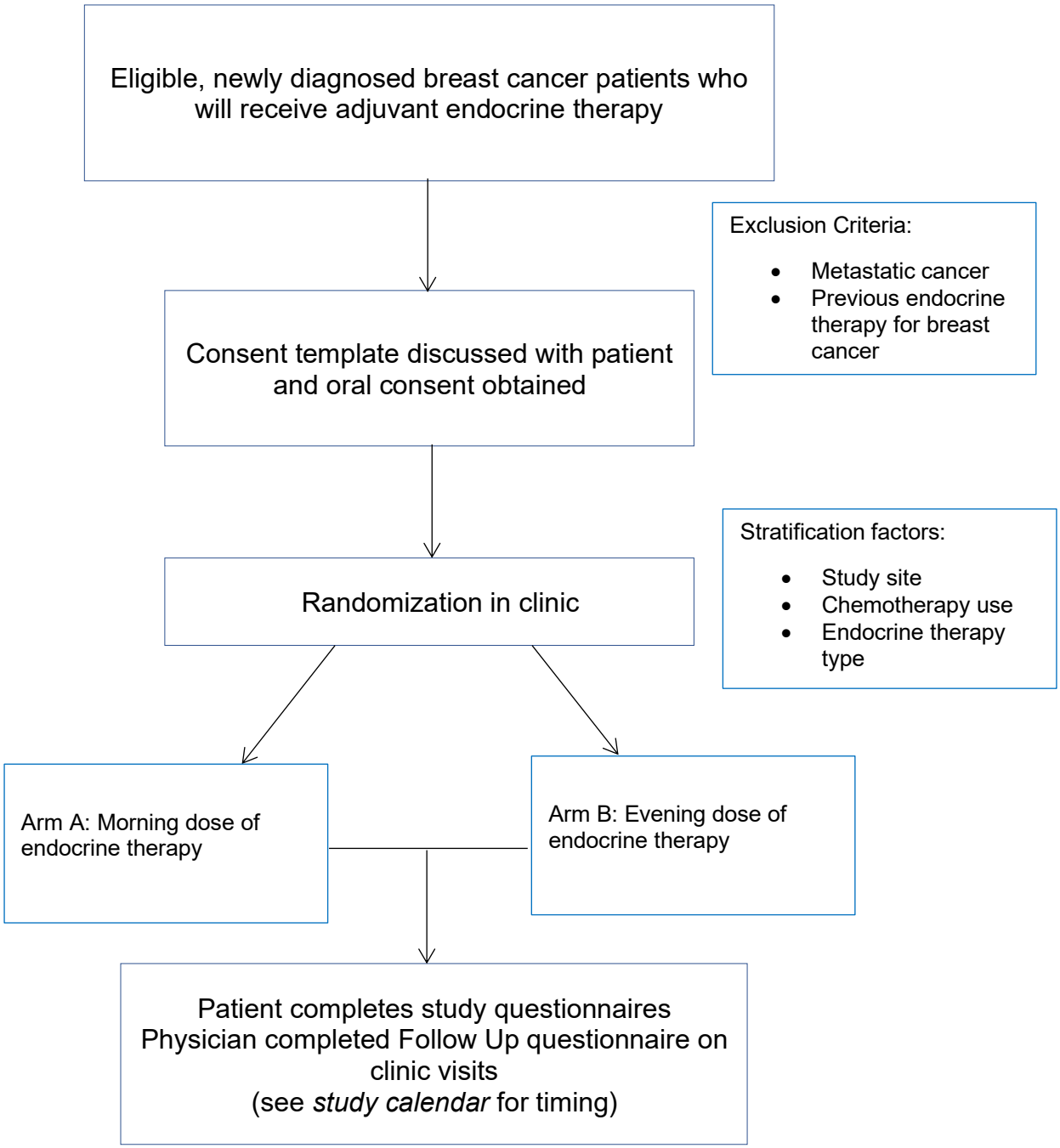

Table 1: Study Calendar

Event	**Screening**	**Baseline**	**4 weeks (± 1 week)**	**8 weeks (±1weeks)**	**12 weeks (± 2 week)**	**52 weeks (± 2 week)**
Initial assessment	X					
Confirmation of Eligibility	X					
Integrated Oral Consent	X					
Randomized to either morning or evening dose of endocrine therapy		X				
Questionnaires - EuroQoL-5D-5L - FACT-B and ES		X	X	X	X	X
Participant Follow up and compliance					X	X
Timing Preference Questionnaire		X				X
Health Care Provider Follow up Questionnaire[1]					X	X

1. To reflect real-world practice, no additional clinic visit will be required, but participants will be contacted by a CRA or a health care provider at 12 weeks and 52 weeks to collect compliance information.

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