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**Official Title:** Identifying ideal reimbursement “dose” to reduce clinical trial-related financial toxicity

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## 1. Background and Significance

Demographically and clinically diverse participants are necessary to ensure breast cancer clinical trial results are generalizable at the population level, yet trial participants rarely represent the real-world population in which the intervention will be applied.[1-5] Breast cancer patients of low socioeconomic status are one population group underrepresented in clinical trials, potentially due to the high out-of-pocket costs associated with trial participation.[6, 7] Direct research costs uncovered by the trial sponsor, such as the trial treatment itself or trial-related labs, imaging, procedures, or out-of-network care, as well as indirect costs of participation, such as travel or time off work, are at the expense of the patient.[8-11] Thus, it's estimated that almost half of patients in early phase oncologic clinical trials spend at least $1,000 per month out-of-pocket to participate.[12] The high out-of-pocket costs associated with trial participation drive underrepresentation of economically vulnerable women with breast cancer in clinical trials and could exacerbate existing inequitable clinical outcomes.[1]

Our previous nationwide survey found 1 in 4 respondents reported payment or support for trial participation, such as transportation, childcare, or paid time off from work, would influence their decision to participate.[13] Thus, reimbursement for trial participation costs could aid in reducing the financial toxicity (defined as high out-of-pocket costs and accompanying financial distress[14]) experienced by trial participants and allow for more diverse trial samples by dismantling recruitment and retention barriers. Reimbursement for clinical trial participation could be particularly impactful for women with breast cancer enrolled in clinical trials at UAB, since this population includes many patients who are Black (who experience an Alabama poverty rate of 28% vs. 12% for White patients[15]) or who travel from rural areas across the state of Alabama to receive care. However, the impact of reimbursement is currently unclear. Thus, the ***critical first step*** in testing the impact of reimbursement is identifying appropriate levels of reimbursement needed to compensate for trial-related out-of-pocket costs. Without such information, breast cancer patients of low socioeconomic status could face barriers to trial participation, preventing them from receiving new, cutting-edge treatment and biasing the evidence base for real-world clinical practice guidelines.

## 2. Preliminary Studies

One in three UAB oncology patients experience financial toxicity. Our study of 1,564 UAB oncology patients found that 29% were experiencing financial distress. Reported distress also differed by race, with 40% of Black patients screened positive for financial distress compared to 23% of White patients. Differences in types of financial difficulties were seen comparing Black and White patients, including 32% vs. 15% reporting difficulty with upfront medical payments and 25% vs. 10% reporting financial difficulties with transportation for care, respectively (*presented at the O'Neal Comprehensive Cancer Center's 22nd Annual Research Retreat*).

Cost-related barriers to care impact clinical trial participation. Our previous study of 3,682 U.S. adult respondents to the Health Information National Trends Survey found that over half (55%) of respondents reported at least one cost-related consideration as very influential to trial participation, including if usual care was not covered by insurance (reported by 42%), payment for participation (24%), or support for participation, such as transportation, childcare, or paid time off from work (24%). Notably, respondents with lower perceived income had double the odds of reporting a cost-related consideration as very influential to trial participation than those with higher perceived income.[13]

Socioeconomic inequities in clinical trial enrollment exist for patients with breast cancer at UAB. In our study of women with breast or ovarian cancer prescribed a therapeutic drug at UAB

(N=512), patients living in neighborhoods of high vs. low disadvantage had similar odds of cancer clinical trial eligibility, interest, and invitation, yet 3.4 times higher odds of declining enrollment, potentially due to financial barriers.[16]

## 3. Study Objectives

2.1 Overall objective and hypothesis: Our overall objective is to ***innovatively use a dose-finding approach*** to identify the recommended reimbursement amount for women with breast cancer enrolled in a clinical trial. We ***hypothesize*** that optimal reimbursement for trial-related expenses will decrease patient financial toxicity and increase trial retention. The ***rationale*** is that understanding the impact of reimbursement for trial-related costs will aid in addressing socioeconomic barriers to trial participation, thus allowing for more diversity in trial enrollment and ensuring equitable efficacy of cancer treatments when used in real-world clinical settings.

2.2 Specific aims: To accomplish this overall objective, we will propose the following specific aims:

**Aim 1. Identify the recommended reimbursement amount in trial-enrolled women with breast cancer experiencing financial toxicity.** We propose a pilot reimbursement dose de-escalation trial (continual reassessment method design; N=30) testing a monthly reimbursement for trial-enrolled patients who screen positive for financial toxicity. We will oversample patients who are Black (50%) or residing in rural locations (50%). Monthly patient-reported financial toxicity and reimbursement acceptability and appropriateness will be captured. Reimbursement dose will start at $1000 and de-escalate if patients find the reimbursement dose suitable (negative financial toxicity screen, reimbursement dose deemed acceptable/appropriate).

**Aim 2. Explore patient perceptions of trial reimbursement amounts.** Using semi-structured interviews, we will explore the effects of reimbursement on (1) specific covered and uncovered trial-related costs, (2) financial toxicity, and (3) current retention and future participation in clinical trials.

## 4. Investigation Plan and Study Procedures

4.1 Study design and population: This will be a prospective, health services research study modeled after a traditional, dose de-escalation phase I trial design. The study population will include women with early stage breast cancer currently enrolled in the Investigation of Serial studies to Predict Your Therapeutic Response with Imaging and Molecular AnaLysis (I-SPY TRIAL 2) or metastatic breast cancer enrolled in any clinical trial at the UAB Medical Oncology Clinic.

4.2 Study duration: Two years.

4.3 Participants and recruitment:

4.3.1 Inclusion criteria: Participants will be women with early stage breast cancer currently enrolled in the Investigation of Serial studies to Predict Your Therapeutic Response with Imaging and Molecular AnaLysis (I-SPY TRIAL 2) or metastatic breast cancer enrolled in any clinical trial at the UAB Medical Oncology Clinic.

4.3.2 Exclusion criteria: Reasons for study exclusion include non-English speakers.

4.3.3 Sampling: Using standard-of-care patient-reported data collected in clinic, eligible patients will have screened positive for financial toxicity using the validated Comprehensive Score for financial Toxicity[14] (COST; scored 0-44, scores < 26 indicate financial toxicity). Eligible patients will be approached during their clinic visit.

4.3.4 Informed consent: Informed consent will be obtained by a study coordinator through an informed consent form if the patient is interested.

4.4 Approach:

4.4.1 Aim 1: We will use the continual reassessment method phase I dose de-escalation clinical trial design under the assumption that financial toxicity may increase when the reimbursement "dose" decreases. Continual reassessment method is a model-based trial design that informs how the reimbursement "dosage" should be adapted for the next patient cohort based on past trial data.[17, 18] The parameters to be used in the continual reassessment method are listed below.

4.4.1.1 Number of doses: We suspect six reimbursement dose amounts will be assessed. However, the number of dose amounts may decrease if a cohort finds their reimbursement dose amount as unsuitable (at least 1 of the 3 de-escalation criteria are not met in 2 patients), in which no dose de-escalation will occur in the next cohort.

4.4.1.2 Target toxicity level: The "toxicity" amount will be set at 40% (de-escalation criteria unmet in 2/5 patients) due to the low-risk nature of the "dose," which is money rather than drug. Note that toxicity in this study is defined as suitability of the reimbursement dollar dose defined by 3 patient-reported measures: (1) financial toxicity (defined as out-of-pocket costs and accompanying psychological distress), (2) acceptability of the reimbursement dose, and (3) appropriateness of the reimbursement dose.

4.4.1.3 Dose-toxicity model: We will use a one-parameter logistic model.

**Table 1. Dose toxicity skeleton.**

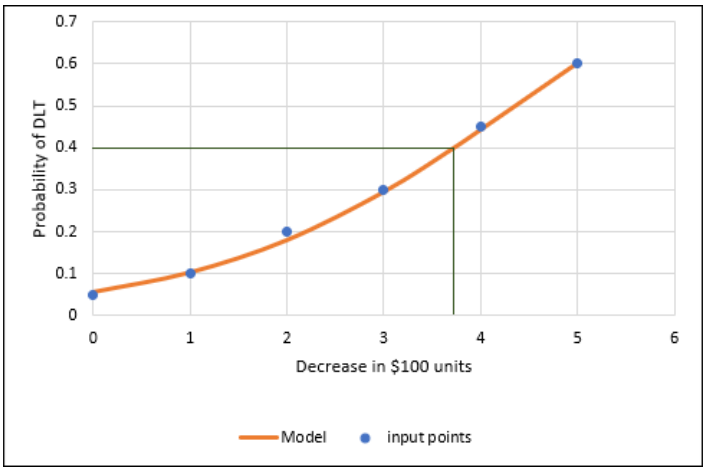
| Dose number | Reimbursement dose amount | Decrease from starting dose in $100 units | Prior probability of dose-limiting toxicity |
|---|---|---|---|
| 1 | $1000 | 0.001 | 0.05 |
| 2 | $900 | 1 | 0.1 |
| 3 | $800 | 2 | 0.2 |
| 4 | $700 | 3 | 0.3 |
| 5 | $600 | 4 | 0.45 |
| 6 | $500 | 5 | 0.6 |

4.4.1.4 Dose-toxicity skeleton: Shown in **Table 1**.

As this is a dose de-escalation trial testing the feasibility of a dollar decrease in reimbursement from a maximum of $1000, we are assessing the minimally tolerated dose. This refers to minimum dollar amount needed to alleviate trial-related financial toxicity for patients participating in I-SPY TRIAL2. With the data fitted to a logistic model, the minimally tolerated dose should be around

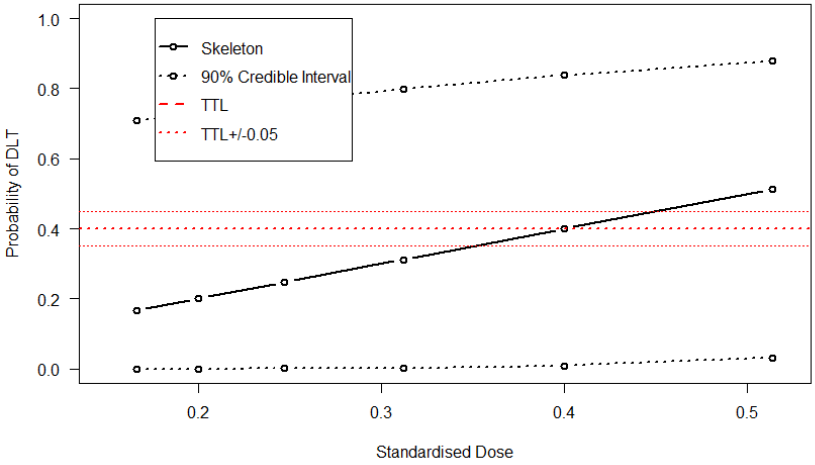
$630 (i.e., a decrease of about $370 from the starting dose of $1000), and we would expect to detect it at the 5th dose (**Figure 1**).

**Figure 1. Number and spacing of doses.**




The operating characteristics also appear fine using a one-parameter logistic model (**Figure 2**).

**Figure 2. Dose-toxicity scenarios.**




4.4.1.5 Method of inference: We will use a Bayesian approach with informative priors.

4.4.1.6 Decision rules: We will choose the reimbursement dose with an estimated probability of a minimally acceptable, appropriate, and financial toxicity-limiting reimbursement dose closest to, but not greater than, the optimal reimbursement level.

4.4.1.7 Sample size and cohort size: Our total sample size for women with early stage breast cancer patients is 30, comprised of 6 cohorts of 5 patients

each. Our total sample size for women with metastatic breast cancer patients is also 30, comprised of 6 cohorts of 5 patients each.

4.4.1.8 Safety modifications: We expect minimal safety concerns with this study, since there is no medical/drug intervention.

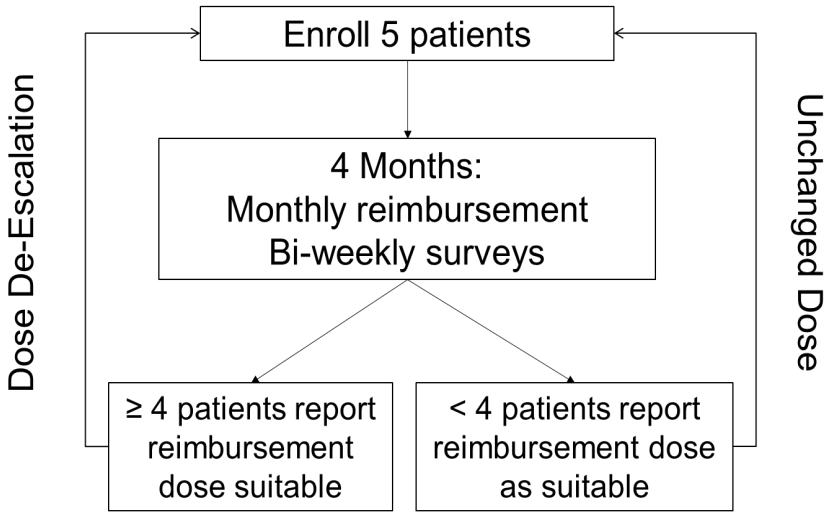
4.4.1.9 Stopping rules: Early termination of phase I trials often occurs if adding additional patients to the trial will not result in changes to the identified optimal dose. As this is not a true phase I trial, but rather a health services pilot feasibility trial anchored within a phase I trial methodological design, no stopping will occur. Enrollment of our targeted 30 patients is necessary to understand our primary feasibility outcomes move our science forward to test outcomes in a larger randomized controlled trial.

4.4.1.10 Patients will be dosed in cohorts of 5, with a maximum available sample size of 30 early stage and 30 metastatic breast cancer patients. The first cohort of 5 patients will be enrolled at the first reimbursement dose level of $1000 per month for 4 months ($4000 per patient in total). Patients will be surveyed biweekly to determine patient financial toxicity (COST tool[19]), acceptability of the reimbursement dose (Acceptability of Intervention Measure[20]), and appropriateness of the reimbursement dose (Intervention Appropriateness Measure[20]). Participants will be surveyed in-person at baseline, then biweekly over the phone. Semi-structured interviews will be completed in-person, with an option for completion virtually if the participant prefers. At the end of the 4-month period, reimbursement dose suitability will be determined as suitable by a cumulative negative financial toxicity screen and reimbursement dose deemed acceptable and appropriate in at least 4 patients (**Table 2**).
If the reimbursement dose is found suitable (all of the 3 criteria are met in at least 4 patients), we will de-escalate the reimbursement dose for the next cohort of 5 patients (**Figure 3**). If the reimbursement dose is found unsuitable (at least 1 of the 3 criteria are not met in 2 patients), the next cohort of 5 patients will be enrolled at the same reimbursement amount ($1000 per month for 4 months). This sequence will continue until 30 patients have received the reimbursement intervention.

**Table 2. Reimbursement dose suitability and de-escalation criteria.**

| Reimbursement Dose Suitability Criteria | Instrument | Scoring | De-Escalation Criteria |
|---|---|---|---|
| Negative financial toxicity screen | COmprehensive Score for financial Toxicity (COST)[19] | Scored 0-44, scores < 26 indicate financial toxicity | Average score ≥ 26 |
| Reimbursement dose acceptable | Acceptability of Intervention Measure (AIM)[20] | 4-item, 5-point Likert scale; higher scores indicate greater acceptability | Average score ≥ 4 |
| Reimbursement dose appropriate | Intervention Appropriateness Measure (IAM)[20] | 4-item, 5-point Likert scale; higher scores indicate greater appropriateness | Average score ≥ 4 |

**Figure 3. Study schema.**




4.4.1.11 Justification of starting dose: The initial $1,000 dose is based on a prior estimate of a logit model with $\beta_0 = -2.79$ and a slope $\beta_1 = 0.64$ for the dose in $100 units. This was based on consensus among the investigators in the study.and data from three studies:

4.4.1.11.1 In a study of 213 patients with cancer enrolled in a phase I trial at MD Anderson, Huey and colleagues found 48% of patients had out-of-pocket costs of at least $1,000 per month.[2]

4.4.1.11.2 In a study of 153 patients with cancer enrolled on a clinical trial and receiving financial assistance through a cancer care equity program at Massachusetts General Hospital, reimbursements averaged $185 per month for patients living in Massachusetts, $300 per month for patients living in New England, and $900 per month for patients living outside of New England.[3]

4.4.1.11.3 In a study of 66 patients with cancer enrolled on a clinical trial and receiving financial assistance through a financial reimbursement program at UCSF and USC, 11% of patients reported incurring out-of-pocket costs of at least $1,000 per month.[4]

Notably, we suspect women with breast cancer receiving care at UAB may have higher out-of-pocket costs associated with clinical trial participation than what was found in these studies due to high poverty rates, uninsurance, long travel distances, and lost productivity. Thus, based on the three studies completed in other US regions, as well as the unique cost-related barriers to trial participation in Alabama-based patients, we do not believe $1,000 per month to be an excessive starting point. As this is a pilot study, there is a chance that the patients will find the $1,000 per month unsuitable. Reasons why the patients find this amount unsuitable will be explored in our qualitative interviews. Due to budgetary constraints of the funding mechanism, we are unable to offer more than $1,000 per month. However, both the quantitative and qualitative data regarding suitability will inform our next study testing reimbursement in a larger sample.

4.4.2 Aim 2: Qualitative, semi-structured interviews will be conducted with patients from Aim 1. Interview questions will explore the effects of reimbursement on (1) specific covered and uncovered trial-related costs, (2) financial toxicity, and (3) current retention and future participation in clinical trials. Interviews will be audio-recorded and transcribed for analysis.

## 5. Data Analysis

5.1 Aim 1

5.1.1 Sample size: A total of 30 women with early stage breast cancer and 30 women with metastatic breast cancer will be recruited for our study. We will oversample patients who are Black (50%) or residing in rural locations (50%) to ensure representation from patient groups routinely underrepresented in clinical trials. As this is a pilot data funding mechanism, it was necessary to balance both sample size and budgetary constraints. After accounting for research staff (research assistant, biostatistician) and study expenses (interview transcription, publication fees), cohort sizes of 5 were the maximum potential size assuming the potential of no de-escalation of the $1,000 per month reimbursement constrained within a 2-year timeframe.

5.1.2 Power: Because this is a pilot study to assess feasibility of trial-related cost reimbursement to be used in a larger phase II trial, no true power calculation is required.[21] Feasibility benchmarks will be defined as 80% retention of patients and retained patients completing at least 75% of bi-weekly surveys while enrolled.

5.1.3 Analysis: Descriptive sociodemographic, survey, and feasibility data will be calculated for all patients. Comparisons by race (white/black) and residence (rural/urban) will be investigated. Mean differences, or effect sizes, will be calculated using Cohen's d or Cramer's V to determine the magnitude of relationships in bivariate associations.[22]

5.2 Aim 2 Analysis: Using a directed content analysis approach,[23] a codebook will be created as guidance. The initial codebook will be reviewed by Dr. Gabrielle Rocque (*collaborator*, medical oncologist) and Dr. Maria Pisu (*collaborator*, health economist). Thematic analysis will be conducted by Dr. Courtney Williams (*PI*) and Ms. Keyonsis Hildreth (*research assistant*, disparities researcher) and used to qualitatively code interview text into codebook categories. Thematic concordance between Dr. Williams and Ms. Hildreth will be reviewed after every 2-3 interviews. If needed, new codes or subcodes will be created based on the data. Newly added codes will be used to create a final codebook. All interview transcripts will be reviewed using the final codebook. Themes by race and residence will be investigated.

5.3 Secondary data analysis: To further understand potential cost and travel burdens to participate in a cancer clinical trial, we will abstract trial and patient data from UAB oncologic therapeutic trial treatment protocols and the OnCore database. Abstracted trial data will include factors associated with financial burden, such as visit frequency and sponsor payment to participants. Abstracted patient data will include sociodemographic and clinical characteristics, such as home address (to map distance/time required to travel to clinic).

## 6. Data and Safety Monitoring

6.1 Safety monitoring: Dr. Williams will be responsible for reviewing and monitoring all study data and any adverse events during data collection. The investigative team will meet with study personnel every 2 weeks to evaluate study progress, including

periodic assessments of data quality and timeliness, participant recruitment, participant risk versus benefit, and other factors that can affect study outcomes. Any unanticipated problems and adverse events will be reported to the UAB IRB according to policies. The risks involved for study participation are minimal and do not put safety at risk.

6.2 Data: Survey responses will be kept within an encrypted, password-protected database and stored in network drives with restricted access on a password protected computer. Data from this study housed at UAB will be destroyed within three years of study completion.

## 7. Benefits

The potential benefits include increased understanding of (1) the optimal reimbursement "dose" to reduce trial-related financial toxicity, (2) specific categories of trial-related expenses that could result in barriers to participation if not reimbursed, and (3) the impact of reimbursement on trial recruitment and retention outcomes. This understanding could benefit patients by reducing the trial-related financial toxicity in women with breast cancer, dismantling trial access barriers, and promoting greater diversity in trial samples.

## 8. Potential Risks and Solutions

- Concern: Reimbursement could be considered as undue influence for research participation.
- Solution: Reimbursement for trial-related expenses is considered a "just and fair," non-coercive practice against patient exploitation by both the US Food and Drug Administration and American Society for Clinical Oncology.[24-26] Coercion to participate in research is unlikely in our study since eligible women will have already enrolled in the I-SPY TRIAL 2.
- Concern: The US Department of Health and Human Services Office of Human Research Protections advises that ethical payments to research participants should not be "excessive."[27]
- Solution: Our calculations assume the highest reimbursement dose is not excessive, but rather allows for participants to reach the break-even point, compensating for incurred trial-related out-of-pocket costs. I-SPY TRIAL 2 participants have weekly infusion treatments for the first 12 weeks of enrollment, followed by 4 cycles of standard chemotherapy every 2-3 weeks, resulting in 16 infusion visits alone. Based on the initial reimbursement dose of $4000 over 4 months, the estimated reimbursement per infusion visit is $250. This would ideally reimburse any medical expenses uncovered by insurance, transportation to and from clinic, parking, food, lodging, caregiver expenses, and lost wages from time off work. Notably, participants also have trial-required scans, labs, biopsies, and surgery, further increasing trial-related costs. Thus, we believe the estimated maximum reimbursement is potentially less than the break-even point.
- Concern: Patients included in this reimbursement dose de-escalation trial will have already been enrolled or enrolling onto a clinical trial, thus biasing the sample towards patients who do not have cost-related barriers to trial participation or who are willing to accept the complete cost of trial participation.
- Solution: Risk of financial toxicity is not fixed and may increase with increasing time on trial. Identifying the optimal reimbursement "dose" may therefore increase likelihood of

not only trial recruitment for individuals with financial barriers, but also trial retention for individuals experiencing trial-related financial toxicity. It is also unclear if patients are informed of or fully understand trial-related costs during trial enrollment. These recruitment and retention outcomes will be explored in our qualitative interviews (Aim 2).

- Concern: Enrollment onto I-SPY TRIAL 2 is too low to accrue patients to this reimbursement dose de-escalation trial.
- Solution: We will expand to other UAB breast cancer clinical trials if necessary.

**9. Confidentiality**

Breach of confidentiality will be minimized by removal of HIPPA-protected information from the dataset, use of secure data transfer, and encrypted data storage on a password-protected computer.

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