# The efficacy of software to help patients understand drug costs for treatment for breast cancer

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## 1. Introduction

All investigators involved in this study shall conduct the research in accordance with the *Declaration of Helsinki* (revised October 2013) and the *Ethical Guidelines for Medical and Health Research Involving Human Subjects* (Ministry of Education, Culture, Sports, Science and Technology / Ministry of Health, Labour and Welfare Notification No. 3, 2014; partially revised February 28, 2017).
This study will be conducted only after obtaining approval from the Institutional Review Board (IRB) of each participating institution and authorization from the head of each institution.

## 2. Background

In recent years, advances in medical science have led to the development of a wide variety of therapeutic agents for breast cancer, thereby expanding treatment options. However, many newly developed anticancer drugs are costly, and the resulting increase in patient financial burden has raised concerns regarding *financial toxicity*. High out-of-pocket medical expenses have been reported to reduce quality of life (QOL) and may cause delays or avoidance of care, potentially leading to worse health outcomes (Refs. 1, 2).
*Shared decision-making (SDM)* is a process in which healthcare providers and patients discuss the advantages and disadvantages of available treatment options, taking into account the patient's values and preferences, to reach a joint decision (Ref. 3). In cancer care, SDM is considered essential, and these discussions are expected to include economic considerations related to treatment.
Despite the recognized importance of discussing the financial aspects of treatment, cost-related communication between healthcare providers and patients rarely occurs in clinical practice (Ref. 4). Reported barriers include insufficient knowledge of drug costs due to the large number of available agents, inadequate training of healthcare professionals, and the ethical belief among clinicians that treatment benefits should not be compromised for financial reasons (Refs. 5, 6).
*ChemoCalc* (Nippon Chemiphar Co., Ltd.) is a software application designed to help physicians and pharmacists provide patients with an estimated drug cost for breast cancer treatment. Using this application, clinicians can easily explain the approximate cost of each regimen on a computer screen without requiring special training or manual cost calculation. This tool is expected to facilitate patient understanding of drug costs.
In a pilot study conducted at Nagasaki University Hospital (Approval No. 17112001), a significantly higher proportion of patients in the ChemoCalc group reported that they understood the drug costs compared with those in the usual-explanation group.

## 3. Study Objectives and Significance

This study aims to determine whether the use of ChemoCalc improves patients' understanding of drug costs compared with standard explanations. In addition to comprehension, we will examine whether ChemoCalc enhances patients' awareness of the importance of drug costs in treatment decision-making. Furthermore, we will evaluate whether using ChemoCalc influences actual treatment selection.
The ultimate goal is to establish an informed consent process that enables attending physicians to engage in shared decision-making while considering patients' financial circumstances.

## 4. Study Methods

### 4.1 Study Design

- **Invasiveness:** None
- **Intervention:** Yes
- **Type of study:** Confirmatory study
- **Study design:** Randomized controlled trial
- **Blinding:** Open-label
-

### 4.2 Study Overview

Eligible patients who meet the inclusion criteria and provide informed consent will be randomly assigned to one of two groups: the *Usual Explanation group* or the *ChemoCalc group*.
In the Usual Explanation group, the attending physician will explain the next treatment using their conventional method. In the ChemoCalc group, the physician will use ChemoCalc to explain the next treatment. The stratification factor will be the cost-awareness questionnaire (Appendix 5).
After the treatment explanation, patients will complete a questionnaire survey. The attending physician will also record the recommended treatment prior to explanation and the final treatment decision after the discussion. After completing the questionnaire, patients in the Usual Explanation group will be provided with the ChemoCalc results.

### 4.3 Overview of the Application

*ChemoCalc* (developed by Nippon Chemiphar Co., Ltd.) is an application designed to help physicians or pharmacists provide patients receiving breast cancer treatment with an approximate estimate of drug costs (Appendix 1).
The application is freely available for download at the following website:
https://www.nc-medical.com/chemiphar_oncology/chemocalc.html

## 4.4 Study Participants: Inclusion and Exclusion Criteria

### Study Population

Eligible patients will be those scheduled to initiate or change systemic therapy for metastatic or advanced breast cancer at one of the following institutions:
Nagasaki University Hospital, National Hospital Organization Nagasaki Medical Center, Nagasaki Atomic Bomb Hospital, National Hospital Organization Saga National Hospital, Oikawa Hospital, and Nagasaki Minato Medical Center.

### Inclusion Criteria

Patients who meet all of the following criteria will be eligible for enrollment:

1. Patients diagnosed with metastatic or advanced breast cancer.
2. Age ≥ 20 years at the time of informed consent.
3. Sex: no restriction.
4. Setting: inpatient or outpatient.
5. Patients scheduled to initiate or change drug therapy for metastatic or advanced breast cancer.
6. Patients presented with two or more treatment options by their attending physician.
7. Patients who have received a full explanation of the study, have adequately understood its contents, and have provided voluntary written informed consent.
8.

**Rationale:**

1–2. Adult patients with metastatic or advanced breast cancer who are capable of making their own treatment decisions.
3. Both males and females may develop breast cancer; therefore, no restriction by sex.
4. Treatment discussions may occur in either inpatient or outpatient settings.
5. The study specifically targets patients with metastatic or advanced breast cancer.
6. To assess, as a secondary endpoint, whether treatment selection changes between groups.
7. To ensure adherence to the principles of the Declaration of Helsinki.

### Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Patients with dementia.
2. Patients not responsible for any drug-related out-of-pocket expenses (e.g., recipients of public assistance).
3. Patients deemed by the principal investigator to be inappropriate for participation in this study.

**Rationale:**

1. Such patients may have difficulty making autonomous treatment decisions.
2. Patients exempt from out-of-pocket drug expenses are not suitable for evaluating cost awareness.
3. To ensure participant safety and appropriate study conduct, investigators must retain discretion to exclude individuals judged to be unsuitable.

## 4.5 Study Period

**Study period:** From the date of approval by the director of each participating institution to September 30, 2025**.**
(**Patient enrollment period:** From the date of institutional approval to December 31, 2024)
(Case report submission: By May 31, 2025)

## 4.6 Schedule and Items for Observation and Data Collection

This study will be conducted in accordance with the schedule outlined below, and relevant examinations and information will be collected accordingly.

| Timing | Registration | Randomization | Explanation Day | 0–3 Weeks After Explanation |
|---|---|---|---|---|
| Medical consultation | Visit 1 | Visit 2 | Visit 2 | Visit 3 |
| Informed consent | ○ | | | |
| Confirmation of patient background | ○ | | | |

| Timing | Registration | Randomization | Explanation Day | 0–3 Weeks After Explanation |
|---|---|---|---|---|
| Pathological findings | ○ | | | |
| Cost questionnaire | ○ | | | |
| Physician's recommended treatment | ○ | | | |
| Scheduling of informed consent discussion | | ○ | | |
| Explanation of drug therapy | | | ○ | |
| Patient questionnaire | | | ○ | |
| Selected drug therapy | | | △ | △ |

○ indicates a required item, and △ indicates an item to be conducted at either of the designated time points.

### 4.7 Items to Be Collected in the Study

- Registration: Institution name, attending physician name, patient background (patient identification code, sex, date of birth, age), date of informed consent, pathological findings (ER, PgR, HER2), cost questionnaire, copayment category, and recommended treatment.
- Randomization: Scheduled date for the discussion of treatment options.
- Questionnaire: (Appendix 2)
- Explanation day or 0–3 weeks after explanation**:** Duration of consultation, and the final treatment selected.

### 4.8 Prohibited Concomitant Drugs/Therapies

None.

### 4.9 Restricted Concomitant Drugs/Therapies

None.

### 4.10 Dose Reduction and Treatment Interruption

Not applicable.

### 4.11 Alternative Treatment Options

Patients who do not participate in this study will receive standard care; participation or nonparticipation will not affect treatment options.

### 4.12 Post-Study Care

After study completion, patients will continue the treatment they have selected.

## 5. Discontinuation Criteria for Individual Participants

### 5.1 Criteria for Discontinuation

- When the participant requests to withdraw from the study.
- When the investigator determines that it is inappropriate for the participant to continue in the study.
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### 5.2 Procedures upon Discontinuation

If any of the above criteria are met, the investigator will discontinue the study for that participant.
The investigator will provide an explanation to the participant as needed.
Following discontinuation, appropriate medical care will be provided to ensure that the participant is not disadvantaged.

## 6. Case Registration and Randomization

Randomization method: Stratified block randomization.
Stratification factors: Cost-score grade from the cost questionnaire and patient age.
Registration method: REDCap.
Institution responsible for registration and randomization:
Department of Surgery, Division of Transplantation and Digestive Surgery,
Nagasaki University Hospital.

## 7. Endpoints

### 7.1 Primary Endpoint

The proportions of responses in both groups to the questionnaire items assessing:

- "Understanding of drug costs," and
- "Understanding of the importance of drug costs in treatment decisions"
  (Questionnaire items 3 and 4).

### 7.2 Secondary Endpoints

- Clarity of the explanation.
- Patient's perceived financial outlook.
- Relief of financial anxiety.
- Ease of understanding of ChemoCalc.
- Discrepancy between physician-recommended and patient-selected treatments.
- Association between COST-score grade, copayment category from the cost questionnaire and treatment selection.

### 7.3 Safety Endpoints

None.

## 8. Target Sample Size

**Target sample size:** 106 patients

**Rationale:**

Based on the pilot study, the median (interquartile range) scores for the questionnaire items (primary endpoints) were as follows:

- *Understanding of drug costs* (Question 3): 2.5 (1.0–4.0) in the Usual Explanation group and 5.0 (4.25–5.00) in the ChemoCalc group.
- *Understanding of the importance of drug costs in treatment decisions* (Question 4): 3.0 (3.0–4.5) in the Usual Explanation group and 5.0 (4.25–5.0) in the ChemoCalc group.

Assuming a two-sided significance level of 2.5% (Bonferroni correction applied) and 90% power, sample size calculation using the Mann–Whitney U test indicated that 94 patients were required.

Allowing for a 10% dropout rate, the target enrollment was set at 106 patients**.**

## 9. Statistical Analysis

### 9.1 General Considerations

(1) Software:

All data analyses will be conducted using SAS, R, or JMP.

(2) Rules for Decimal Places:

No rounding will be performed during calculations.

The number of decimal places reported for continuous data will be determined based on the data characteristics and journal submission guidelines to avoid unnecessary complexity.

Percentages will be rounded to one decimal place (second decimal place rounded off).

P-values will be rounded to three decimal places (fourth decimal place rounded off).

(3) Summary Statistics:

Unless otherwise specified, the following will be presented:

- For continuous variables: number of cases, median, mean, standard deviation, minimum, maximum, 25th percentile, and 75th percentile.
- For categorical variables: number of cases and percentage.

(4) Significance Level and Adjustment for Multiplicity:

The significance level will be set at 5%.

For the primary analysis, the Bonferroni method will be used to adjust for multiplicity.

(5) Handling of Missing Data:

No imputation of missing data will be performed.

### 9.2 Definition of Analysis Populations

The analysis populations and their definitions are as follows.

The analysis populations will be illustrated in a flowchart in accordance with the CONSORT statement**.**

| Analysis Population | Definition |
|---|---|
| Registered Cases | All participants enrolled in this study. |
| Intention to Treat (ITT) | All participants who were registered in the study. |
| Full Analysis Set (FAS) | Among the registered cases, all participants who completed the questionnaire survey. |

## 9.3 Analysis of Demographic Data

[Analysis Population] ITT, FAS
[Content] Patient background characteristics will be summarized using descriptive statistics.

## 9.4 Efficacy Analysis

**Primary Analysis**
[Analysis Population] FAS
[Content]
For the five-point Likert scale questionnaire items assessing patients' understanding of drug costs (Question 3) and understanding of the importance of drug costs in treatment decisions (Question 4), statistical comparisons between the Usual Explanation group and the ChemoCalc group will be performed using the Mann–Whitney U test.
A significant difference in both Question 3 and Question 4 will be interpreted as indicating a difference in patients' understanding of the importance of drug costs.

**Secondary Analysis**
[Analysis Population] FAS
[Content]
Exploratory analyses will be performed for the secondary endpoints described in Section 7.2.

# 10. Informed Consent

## 10.1 Method of Obtaining Consent

Investigators shall provide potential participants with the written informed consent form approved by the head of each participating institution.
They will explain the study both orally and in writing, offer sufficient opportunity for questions, and allow adequate time for the participant to decide whether to consent.
After confirming that the participant has fully understood the study, voluntary written consent will be obtained.

## 10.2 Procedures upon Withdrawal of Consent

If a participant withdraws consent to participate in the study, the investigator shall ask the participant to sign a withdrawal form to confirm the withdrawal.
The investigator shall record the withdrawal in the participant's medical record.
Data from participants who withdraw consent will be excluded from all analyses.

# 11. Expected Benefits and Risks (Adverse Events / Complications)

## 11.1 Expected Benefits

Participants in this study, regardless of group allocation, will have access to information on estimated drug costs calculated by *ChemoCalc*.
In addition, it is anticipated that participants will have opportunities to discuss financial issues with their attending physicians.
If the usefulness of ChemoCalc in improving understanding of drug costs is demonstrated, the findings are expected to contribute to enhancing patient education and communication regarding drug expenses in the future.

## 11.2 Expected Risks or Burdens

Participants will be required to spend approximately 15 minutes completing the questionnaire.

## 11.3 Anticipated Adverse Events / Complications

None.

# 12. Study Termination or Discontinuation

The Principal Investigator will review the feasibility of continuing the study if any of the following conditions apply:

- Difficulty in enrolling participants, making it unlikely that the planned sample size can be achieved.

If the Principal Investigator determines that the study should be terminated or discontinued based on any of the following conditions, the decision and a summary of the study results will be promptly reported to the head of the participating institution:

- It becomes evident that continuation of the study no longer has medical or scientific significance.
- The planned study period has been completed.

## 13. Handling of Personal Information and Study Data

### 13.1 Protection of Personal Information

All individuals involved in this study, including external collaborators, shall comply with all applicable laws and regulations concerning the protection of personal information.
They shall make every effort to safeguard participants' privacy and personal data, and shall not disclose any confidential information obtained in the course of the study without legitimate justification. This obligation shall continue even after the individual's involvement in the study ends.
When presenting or publishing study results, care will be taken to ensure that no personally identifiable information is disclosed.
All data collected for this study will be assigned a study-specific identification code unrelated to personal identifiers and will be stored and managed securely in the Department of Transplantation and Digestive Surgery, Nagasaki University Hospital.
A correspondence table linking the identification code to individual participants will be created but will not be taken outside the institution.

### 13.2 Storage Period and Location of Study Data

All data obtained in this study will be stored at Nagasaki University Hospital in accordance with the following provisions.
The data will be retained for at least the minimum period specified below and, if feasible, for as long as possible thereafter.

| Type of Material | Storage Period | Storage Media | Storage Location |
|---|---|---|---|
| Ethics Committee Documents | 5 years after study completion | DVD-R (some in paper format) | Locked storage cabinet (Department of Transplantation and Digestive Surgery, Nagasaki University Hospital) |
| Study-Related Information and Materials | 5 years after study completion | Paper documents, DVD-R | Locked storage cabinet (Department of Transplantation and Digestive Surgery, Nagasaki University Hospital) |
| Correspondence Table | 5 years after study completion | Paper documents | Locked storage cabinet (Department of Transplantation and Digestive Surgery, Nagasaki University Hospital) |
| Records Related to Information Disclosure | 5 years after study completion | Study protocol | Locked storage cabinet (Department of Transplantation and Digestive Surgery, Nagasaki University Hospital) |

**Additional Details on Study Document Storage**

- **Ethics Committee Documents:**
  Copies of application forms, notification letters from the head of the institution, and copies of various submitted or reported documents.
- **Study-Related Information and Materials:**
  All materials that substantiate the data used in this study, including consent forms, questionnaires, test results, research data, data correction logs, and analysis results.
  Each collaborating research site shall also retain the following for a minimum of five years after study completion**:** ethics committee documents, study-related materials (including copies of materials provided to other sites), and correspondence tables.
  The storage media and location shall comply with the regulations of each collaborating institution.

### 13.3 Methods for Disposal of Study Data and Materials

All study-related data and materials shall be disposed of appropriately in accordance with the regulations of each participating institution.

### 13.4 Methods for Data Provision

Researchers at the collaborating institutions will register cases using the Electronic Data Capture (EDC) system.
Original copies of the questionnaires shall be sent to the Department of Transplantation and Digestive Surgery (submission office) by postal mail or as email attachments. Copies shall be retained at each participating site.
Each dataset provided will be assigned an identification code unrelated to personal identifiers.
The providing institution will maintain a correspondence table linking identification codes to individual participants, but this table will not be shared and will be securely stored within the institution.
Based on the case registration forms entered in the EDC, randomization will be performed, and the treatment cost calculation sheet will be sent as an email attachment to the collaborating investigator.

## 13.5 Records of Data Transfer and Receipt

This study protocol itself shall serve as the Record of Data Provision.
The Principal Investigator shall retain this record in accordance with the provisions specified in Section 13.2 (Storage Period and Location of Study Data).
Nagasaki University Hospital, as the receiving institution, shall assume responsibility for preparing and storing such records on behalf of the providing institutions.
However, if any providing institution has its own specific regulations regarding recordkeeping, those regulations shall take precedence, and the institution shall handle the records appropriately in accordance with them.

| Item | Content |
|---|---|
| Information Recipient Institution | Nagasaki University Hospital |
| Principal Investigator (Information Recipient) | Susumu Eguchi, Department of Transplantation and Digestive Surgery |
| Collaborating Institutions / Principal Investigators (Information Providers) | Nagasaki Medical Center — Shigeki Minami<br>Nagasaki Atomic Bomb Hospital — Hideaki Taniguchi<br>National Hospital Organization Saga National Hospital — Hiroki Moriuchi<br>Oikawa Hospital — Masahiro Oikawa<br>Nagasaki Minato Medical Center — Kosho Yamanouchi |
| Items of Information | Refer to the data items listed in Section 4.7 (“Items to Be Collected in the Study”). |
| Source of Information | Information newly collected at each participating institution in accordance with the study protocol. |

## 13.6 Handling of Data upon Withdrawal of Consent During the Study

If a participant withdraws consent during the study, all data related to that participant will be excluded from the analysis set.

## 14. Handling of Deviations from the Study Protocol

If an explanation is provided without using ChemoCalc in the ChemoCalc group, or if ChemoCalc is used in the Usual Explanation group, such cases will be regarded as protocol deviations and excluded from the primary analysis.
Minor deviations from the study protocol that do not affect the primary analysis will be included in the analysis.
Any case involving a violation of ethical guidelines for medical research will be excluded from the study.

## 15. Amendments to the Study Protocol and Related Documents

Any modification or revision of this study protocol or the informed consent form must be approved in advance by the head of the main institution.
After obtaining such approval, the Principal Investigator will promptly notify all collaborating sites of the change.
Upon notification, the responsible investigators at the collaborating institutions shall proceed with the amendment procedures in accordance with their institutional regulations.
No study activity based on the revised protocol, nor any explanation to participants regarding revised content, shall be conducted until approval is obtained from the head of each participating institution.

## 16. Costs to Participants

All examinations and procedures in this study are covered by standard medical insurance; therefore, participation in the study will not increase the financial burden on participants.
No honorarium or transportation reimbursement will be provided for participation.

## 17. Study Registration and Publication of Results

### 17.1 Study Registration

Prior to initiation, the Principal Investigator will register a summary of the study with the University Hospital Medical Information Network (UMIN).
Updates will be made as needed in accordance with protocol amendments or study progress.

### 17.2 Publication of Study Results

Upon completion of the study, the Principal Investigator will publish the results after taking all necessary measures to protect the rights and interests of the participants, their families, and all investigators.
Participant confidentiality will be strictly maintained.

### 17.3 Disclosure to Participants

If a participant or their legal representative requests disclosure of personal information related to the participant, the head of the institution shall promptly respond.
A legal representative may include the participant's spouse, parents, adult children, adult siblings or grandchildren, grandparents, cohabiting relatives, or other individuals deemed equivalent (excluding minors).

## 18. Ownership of Study Results

Although this study may potentially lead to patents or economic benefits, such rights will belong to the research institutions and investigators conducting the study.
Participants will not hold any rights to these outcomes.
All research results derived from this study protocol will belong to the Department of Transplantation and Digestive Surgery, Nagasaki University Hospital**.**

## 19. Research Funding and Conflict of Interest

### 19.1 Research Funding

This study will be conducted using research funds from the Department of Transplantation and Digestive Surgery, Nagasaki University Hospital**.**

### 19.2 Conflict of Interest

There are no potential conflicts of interest that could influence the design, conduct, or interpretation of this study.
All investigators involved will comply with the conflict of interest management policies of their respective institutions, submit necessary disclosures, and obtain approval from the institutional Conflict of Interest Review Committee.

## 20. Monitoring and Auditing

### 20.1 Monitoring

Because this study is non-invasive, monitoring will not be conducted.

### 20.2 Auditing

Because this study is non-invasive, auditing will not be conducted.

## 21. Study Organization

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- Nagasaki Atomic Bomb Hospital — Hideaki Taniguchi
- National Hospital Organization Saga National Hospital — Hiroki Moriuchi
- Oikawa Hospital — Masahiro Oikawa
- Nagasaki Minato Medical Center — Kosho Yamanouchi

## 22. Attachments and Appendices

- **Appendix 1:** Drug Cost Calculation Sheet
- **Appendix 2:** Patient Questionnaires (A and B)
- **Appendix 3:** Case Registration Form (EDC)
- **Appendix 4:** Post-Study Report (EDC)
- **Appendix 5:** Japanese Version of the Cost Awareness Questionnaire

## 23. References


1. Zafar SY, Peppercorn JM, Schrag D et al. (2013) The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expense and insured cancer patient's experience. Oncologist 18:381-90.
2. Richman IB, Brodie M. (2014) A national study of burdensome health care costs among non-elderly Americans. BMC Health Serv Res 14:435.
3. Hoffmann TC, Montori VN, Mar CD. (2014) The connection between evidence-based medicine and shared decision making. JAMA 312.
4. Alexander GC, Casalino LP, Meltzer DO (2003) Patient-physician communication about out-pocket costs. JAMA 290:953-8.
5. Zafar SY, Tulsky JA, Abernethy AP (2014) It's time to have 'the talk': cost communication and patient-centered care. Oncology (Williston Park). 28:479-80.
6. Riggs KR, Ubel PA (2014) Overcoming barriers to discussing out-of-pocket costs with patients. JAMA Intern Med 174: 849-850.