Health Technology Assessment (HTA)

HTA Protocol

Title	Treatment duration of trastuzumab in HER2-positive early breast cancer
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Technology	Trastuzumab (with or without Pertuzumab)
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Conflict of Interest: the authors declare no conflict of interest.

Executive Summary

Background: With an average of 6,200 new cases per year, breast cancer is the most common type of cancer in Swiss women. Up to 15-20% of women with breast cancer have tumours that have an overexpression of the HER2 protein, a protein associated with uncontrolled cell growth in breast cancer. In Switzerland trastuzumab and pertuzumab, pharmaceuticals that bind to the HER2 receptor and prevent the cancer cells from growing and dividing, have been approved in adjuvant and neoadjuvant treatment settings. The approved duration of treatment with trastuzumab in patients with HER2-positive early breast cancer is maximally 12 months or until disease recurrence. Through a health technology assessment (HTA), the question whether a reduced treatment duration of 6 months or less of trastuzumab or trastuzumab combined with pertuzumab is non-inferior in terms of clinical efficacy and has the potential of reducing adverse effects and treatment costs compared with a treatment duration of 12 months will be addressed.

Objective: The objective of this HTA protocol is to define the key questions that will be addressed in the full HTA report, the population, intervention, comparator, and outcomes (PICO) of interest and the planned methodology of the full HTA report.

Methods: For the clinical assessment, a systematic literature search will be conducted in Medline, Embase, Cochrane Library and Cochrane Central Register of Controlled Trials (CENTRAL), and in the International Network of Agencies for Health Technology Assessment (INAHTA) database. Eligible studies will be randomised controlled trials (RCTs) that compared the treatment duration of 6 months or less of trastuzumab or trastuzumab combined with pertuzumab with a treatment duration of 12 months in HER2-positive early breast cancer.

Data will be extracted on study design and characteristics, participant characteristics, intervention and comparator characteristics, and outcome data. The risk of bias of the included RCTs will be assessed using the Cochrane Risk of Bias 2 tool. The certainty of evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Meta-analyses will be conducted for all outcomes relevant to this HTA, if more than one study contributes data to the respective outcome and if the available data are methodologically and clinically appropriate. The plan is to investigate non-inferiority of ≤ 6 months versus 12 months of trastuzumab

or trastuzumab combined with pertuzumab treatment for the outcomes disease-free survival (DFS) and overall survival (OS), and superiority of ≤ 6 months versus 12 months treatment for all other relevant outcomes (e.g., cardiotoxicity). After consultation with clinical experts, it has been decided that as non-inferiority margin an absolute risk difference of 3% for the efficacy outcomes DFS and OS will be considered. In sensitivity analyses, lower (2% absolute risk difference) and higher (4% absolute risk difference) margins will be investigated.

The economic assessment will consist of a systematic literature review of existing health economic evidence, the development of a *de novo* model-based cost-effectiveness analysis for Switzerland, and a budget impact analysis. Swiss epidemiological data on early breast cancer incidence will be combined with the estimated cost difference between the different treatment durations to estimate the yearly budget impact of switching from 12 months of trastuzumab treatment to a treatment duration of 6 months.

To address ethical, legal, social, and organizational issues relating to the different treatment durations, an exploratory literature search will be conducted. The main issues identified will be reported descriptively.

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Abbreviations and acronyms

ADCC	Antibody-Dependent Cellular Cytotoxicity
AdViSHE	Assessment of the Validation Status of Health-Economic decision model
AJCC	American Joint Commission on Cancer
CENTRAL	Cochrane Central Register of Controlled Trials
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss Francs
CI	Confidence Interval
DFS	Disease Free Survival
EBPI	Epidemiology, Biostatistics and Prevention Institute
ECPM	Institute of Pharmaceutical Medicine
ELSI	Ethical, Legal, and Social Issues
ELSO	Ethical, Legal, Social, and Organizational
ESMO	European Society for Medical Oncology
EUnetHTA	European Network for Health Technology Assessment
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HER-2	Human Epidermal growth factor Receptor 2
HORG	Hellenic Oncology Research Group
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
INAHTA	International Network of Agencies for Health Technology Assessment
ITT	Intention-To-Treat
MD	Mean Difference
MeSH	Medical Subject Headings
NB	Nota Bene (= mark well)

NHSEED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NICER	National Institute for Cancer Epidemiology and Registration
OS	Overall Survival
PHARE	Protocol for Herceptin as Adjuvant therapy with Reduced Exposure
PICO	Population, Intervention, Comparator, Outcome
PP	Per-Protocol
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCTs	Randomised Controlled Trials
RoB	Risk-of-Bias
RR	Risk Ratio
SMD	Standardized Mean Difference
SoF	Summary of Findings
TNM	Tumour-Node-Metastasis
UICC	Union for International Cancer Control
UK	United Kingdom

Objective of the HTA Protocol

Based on a preliminary screening of the literature, the objective of the present health technology assessment (HTA) protocol is to formulate the research questions for the HTA on treatment duration of trastuzumab in HER2-positive early breast cancer. The document defines the population, intervention, comparator, outcomes (PICO). It describes the methodology to conduct a systematic literature search, extract, analyse, and synthesise the data in the HTA report on the topic. Research questions are defined, addressing the main HTA domains, i.e., efficacy/effectiveness/safety, costs/budget impact/cost-effectiveness, ethical/legal/social and organisational issues.

1 Policy question

Each health technology assessment (HTA) topic entails a policy question and a research question. In healthcare, a ***policy question*** is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses an existing controversy around a technology. The planned HTA will address the following policy question brought forward by the applicant: “Is ≤ 6 months non-inferior to 12 months adjuvant trastuzumab in patients with HER2-positive early breast cancer?”

Trastuzumab is a treatment for human epidermal growth factor receptor (HER2)-positive breast cancer approved by Swissmedic since 1999 in the metastatic setting.[1 2] Treatment with trastuzumab is currently also approved for patients with early breast cancer until disease recurrence or for a total of 12 months. The costs for trastuzumab are covered by the mandatory health insurance. In early breast cancer with high risk of recurrence trastuzumab is also approved in combination with pertuzumab (another HER2-directed pharmaceutical).[2] In these patients, confirmation by the health insurance is a prerequisite for cost coverage.

The aim of the (planned) full HTA report is to evaluate available data on the question whether a reduced treatment duration of 6 months or less of trastuzumab or trastuzumab combined with pertuzumab is non-inferior in terms of clinical efficacy and has the potential of reducing adverse effects and treatment costs compared with a treatment duration of 12 months in patients with HER2-positive breast cancer. The findings of this assessment will support decision making regarding cost coverage by the mandatory health insurance in Switzerland.

2 Medical background

2.1 Disease epidemiology

With an average of 6,200 new cases per year between 2013 and 2017, breast cancer was the most common type of cancer in Swiss women. During the same period, breast cancer resulted in approximately 1,400 deaths per year.[3] A woman's risk of developing breast cancer and dying from breast cancer in her lifetime was 11.6% and 2.4%, respectively.[3] More than 80% of the affected women survive for more than 5 years after diagnosis.[3]

A major driver of aggressive tumour development and metastasis in women with breast cancer is an overexpression of the HER2 protein.[4] The HER2 protein is a protein that is associated with uncontrolled cell growth and high levels of HER2 protein are found in up to 15-20% of women with breast cancer.[1 4–7]

2.2 Disease diagnosis, symptoms, and treatment options

The most frequent symptoms of breast cancer are a new lump in the breast or armpit, nipple abnormalities (rash, redness, change in appearance, discharge of fluid), changes in breast size or shape, and breast pain.[8–10] However, some people do not have any clinical signs or symptoms at all.[8–10]

The diagnostic process usually consists of physical examination, imaging (e.g., mammography, breast magnetic resonance imaging or ultrasound), and pathological examination. The identified breast cancer is usually characterized according to the Tumour-Node-Metastasis (TNM) classification on cancer staging, jointly developed by the American Joint Commission on Cancer (AJCC) and the Union for International Cancer Control (UICC).[11] The TNM system classify cancers according to the tumour size and location (TX, T0, T1, T2, T3, T4), the lymph node status (NX, N1, N2, N3, N4), and the presence of metastases (MX, M0, M1). The TNM system can be used to classify breast cancer in stages (IA, IIA, IIB, IIIA, IIIB, IIIC, IV).[12] Clinicians often refer to stage I to stage IIA cancer as “early stage” and stage IIB to III as “locally advanced”. However, some clinical studies define patients up to stage IIIA as patients with early breast cancer,[13 14] while others do not provide a definition for early breast cancer in terms of stages.[15–18] Other information included in the diagnosis is oestrogen-receptor and progesterone-receptor status, HER2 status and the grade as measure of cancer cell differentiation.[19 20]

Treatment options for patients with HER2-positive breast cancer include surgery, HER2-directed therapy, chemotherapy, endocrine therapy, and radiation therapy.[21] The combination of treatments, and the order in which to receive them, varies depending on a patient’s specific situation. Chemotherapy may be administered after surgery (adjuvant chemotherapy) or before surgery (neoadjuvant chemotherapy) with the goal of shrinking the tumour or stopping the spread of cancer. Surgery may include mastectomy or breast conserving and axillary surgery.[22]

3 Technology description

3.1 Technology description

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that binds to the HER2 protein, inhibiting cancer cell growth and division, and mediating antibody-dependent cellular cytotoxicity (ADCC).[23–25] In patients with HER2-positive early breast cancer, trastuzumab in combination with chemotherapy has been shown to be significantly more effective than chemotherapy alone.[26 27] For example, Moja et al. reported that trastuzumab-containing treatment regimens compared to chemotherapy alone have a HR of 0.66 for OS (95% confidence interval (CI) 0.57 to 0.77, p<0.00001) and a HR of 0.60 for DFS (95% CI 0.50 to 0.71, p<0.00001), respectively.[26]

Similarly, in another meta-analysis, the relative risk of breast cancer recurrence and death from breast cancer in patients treated with trastuzumab plus chemotherapy versus chemotherapy alone were estimated to be 0.66 (95% CI 0.62 to 0.71; p<0.0001) and 0.67 (95% CI 0.61 to 0.73; p<0.0001), respectively.[27] The average absolute reduction in 10-year risk of recurrence was reduced by 9.0% points and breast cancer mortality was reduced by 6.4% points.[27]

Several trastuzumab-containing drugs are approved by Swissmedic.[2] The first drug entering the Swiss market was Herceptin® by Roche Pharma AG, which was approved in 1999 by Swissmedic and entered the list of specialties (reimbursement list) held by the Federal Office of Public Health (FOPH) in 2002. Biosimilars to Herceptin® were approved after 2019 (e.g., Herzuma®, Kanjinti®, Ogivri®, Trazimera®).[2]

Pertuzumab (Perjeta®) has been approved by Swissmedic in 2012 and is on the list of specialities since 2015 (temporary admission until 2024).[2]

3.2 Dosage, administration, treatment duration, and indications

Depending on the treatment scheme, patients are treated either weekly or every three weeks, with loading doses for the first cycle of ether 4 mg/kg body weight or 8 mg/kg body weight, respectively, and a maintenance dose of either 2 mg/kg body weight or 6 mg/kg body weight, respectively. Most trastuzumab-containing drugs are administered through intravenous infusion. Herceptin subkutan® is the only available subcutaneous formulation. Treatment duration in HER2-positive early breast cancer patients is approved until disease recurrence or for a total of 12 months).[28 29] In Switzerland, Swissmedic has approved trastuzumab for adult patients with HER2-positive early breast cancer:[28]

- following surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy (if applicable);

- following adjuvant chemotherapy with doxorubicin and cyclophosphamide in combination with paclitaxel or docetaxel;

- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin;

- in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab in case of locally advanced disease or tumours with a diameter > 2cm (higher risk of recurrence).

In patients with HER2-positive early breast cancer with high recurrence risk, or locally advanced inflammatory breast cancer, trastuzumab is also approved in combination with pertuzumab as adjuvant or neoadjuvant treatment for a total treatment duration of 12 months. Pertuzumab is approved in combination with trastuzumab (prescribed as a separate drug [Perjeta®] or as a fixed-dose combination [Phesgo®]).[28]

Trastuzumab is also approved for metastatic HER2-positive breast cancer, HER2-positive gastric cancer, and HER2-positive gastro-oesophageal carcinoma, which are not part of the planned HTA report.[28]

In the adjuvant treatment setting, twelve months of trastuzumab, chosen by expert consensus, has been considered the standard treatment based upon the drug approval trial HERA for Herceptin® in 2005.[30] [31] The HERA trial also demonstrated that extending trastuzumab to 24 months was not significantly different than treatment over 12 months in terms of DFS (HR 0.99, 95% CI 0.85 to 1.14, p=0.86), but increased side effects, namely cardiotoxicity (20.4% versus 16.3%).[30] [31] Since then efforts to de-escalate treatment have been ongoing to decrease side effects such as cardiotoxicity but also costs associated with treatment.

3.3 Contraindications

Trastuzumab should not be used to treat people with HER2-negative breast cancer. Herceptin is contraindicated in patients with known hypersensitivity to trastuzumab, Chinese hamster ovary (CHO) cell protein or any of the excipients of the medicinal product. Herceptin and anthracyclines should not be administered concomitantly in adjuvant treatment. In neoadjuvant treatment, concomitant administration of Herceptin and anthracyclines should be used with caution and only in chemotherapy-naïve patients. Herceptin is contraindicated in patients who have resting dyspnoea due to their advanced malignancy or comorbidities.[32]

4 PICO questions

Population, intervention, comparator, and outcomes (PICOs) are defined as:

PICO 1:

P:	Adult patients with HER2-positive early (including locally advanced operable) breast cancer
I:	Adjuvant or neoadjuvant trastuzumab treatment, ≤ 6 months treatment duration
C:	Adjuvant or neoadjuvant trastuzumab treatment, 12 months treatment duration
O:	- overall survival (OS) - disease free survival (DFS) - health-related quality of life (HRQoL) (measured through a validated scale) - treatment-related adverse effects: diarrhea, rash, nausea, vomiting, fatigue - serious treatment-related adverse effects: cardiac toxicity (congestive heart failure, left ventricular ejection fraction), bone loss/osteoporosis, vision/eye problems - costs - budget impact - cost-effectiveness

PICO 2:

P:	Adult patients with HER2-positive early (including locally advanced operable) breast cancer *
I:	Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, ≤ 6 months treatment duration
C:	Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, 12 months treatment duration
O:	- overall survival (OS) - disease free survival (DFS) - health-related quality of life (HRQoL) (measured through a validated scale) - treatment-related adverse effects: diarrhea, rash, nausea, vomiting, fatigue - serious treatment-related adverse effects: cardiac toxicity (congestive heart failure, left ventricular ejection fraction), bone loss/osteoporosis, vision/eye problems - costs - budget impact - cost-effectiveness

* Combination treatment with pertuzumab and trastuzumab is currently restricted in Switzerland to the adjuvant treatment of HER2-positive breast cancer patients with high risk of recurrence (i.e., tumour size > 2 cm or lymph node-positive) and to the neoadjuvant therapy of HER2-positive breast cancer patients with locally advanced inflammatory breast cancer or with high risk of recurrence (i.e., tumour size > 2 cm or lymph node-positive).

5 HTA key questions

5.1 HTA key questions

For the evaluation of the technology the following research questions covering central HTA domains, as designated by the EUnetHTA Core Model (clinical efficacy, safety, costs, cost-effectiveness, budget impact, ethical, legal, social, and organizational aspects), are addressed:

1. Is adjuvant or neoadjuvant trastuzumab treatment (with or without pertuzumab) for ≤ 6 months non-inferior in terms of clinical efficacy to 12 months treatment in women with early breast cancer?
2. Is adjuvant or neoadjuvant trastuzumab treatment (with or without pertuzumab) for ≤ 6 months superior in terms of safety compared to 12 months treatment in women with early breast cancer?
3. What are the estimated annual costs of trastuzumab treatment (with or without pertuzumab) in the specified population?
4. What is the budget impact of reducing treatment costs from 12 to ≤ 6 months?
5. Is ≤ 6 months treatment with adjuvant or neoadjuvant trastuzumab treatment (with or without pertuzumab) cost-effective compared to 12 months treatment?
6. Are there ethical, legal, social or organisational issues related to the reduction of the treatment duration?

5.2 Additional question(s)

7. None.

6 Methodology

6.1 Clinical assessment

The HTA protocol for the clinical assessment is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[33]

During the preparation of this HTA protocol, Swiss clinical experts (n=3) were consulted to receive their input on the planned methodological approach (i.e., detailed eligibility criteria, definition of outcomes of interest, definition of non-inferiority margin) and their overall feedback on the protocol. These experts will be involved and consulted for feedback throughout the conduct of the HTA.

6.1.1 Databases and search strategy

A systematic literature search for eligible RCTs in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the International Network of Agencies for Health Technology Assessment (INAHTA) databases will be conducted. The search will be based on medical subject headings (MeSH) and keywords related to the concepts of “breast cancer”, “(neo)adjuvant chemotherapy”, “trastuzumab" and "pertuzumab", and "randomized controlled trial”. The search for studies on trastuzumab will include a search concept for “treatment duration” (i.e., the comparison of interest), while the search for studies on pertuzumab will not in order to increase sensitivity. This is, because the relative treatment duration for pertuzumab may be described less explicitly than for trastuzumab in studies involving the co-administration of pertuzumab and trastuzumab. The published sensitivity- and precision-maximizing search filter for RCTs by the Cochrane Collaboration will be used, but search terms for "placebo" will be excluded, which do not apply in the context of this HTA.[34] The search strategies are detailed in the Appendix 9.1. In addition, ClinicalTrials.gov and the World Health Organization (WHO) Clinical Trials Registry will be searched for records of further non-reported, planned or ongoing studies. All databases will be searched from inception. Reference lists of identified systematic reviews and HTA reports as well as other relevant publications will be screened for additional records of potentially relevant primary studies.

6.1.2 Inclusion/exclusion criteria and study selection

Table 1 summarizes the inclusion and exclusion criteria that were defined according to the PICO criteria.

Table 1 Study inclusion and exclusion criteria for the clinical assessment.

Criterion	Inclusion	Exclusion
Publication period	No restriction	-
Publication status	Published full text available.	Full text not available.
Language	English, German, French, Italian.	All other languages
Setting/Location	No restriction.	-
Study design	RCT.	Not RCT.
Population	Females or males (≥18 years) with early breast cancer.	Females or males without breast cancer or with advanced breast cancer. Animal studies
Intervention	PICO 1: Adjuvant or neoadjuvant trastuzumab treatment, ≤ 6 months treatment duration. PICO 2: Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, ≤ 6 months treatment duration.	Other drugs for the treatment of early breast cancer.
Comparator	PICO 1: Adjuvant or neoadjuvant trastuzumab treatment, 12 months treatment duration. PICO 2: Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, 12 months treatment duration.	Other drugs for the treatment of early breast cancer (except as co-treatments used equally in all relevant study arms). No drug treatment / placebo.
Outcomes	Overall survival Disease free survival Health-related quality of life Adverse effects: diarrhea, rash, nausea, vomiting, fatigue Serious adverse effects: cardiac toxicity (congestive heart failure, left ventricular ejection fraction), bone loss/osteoporosis, vision/eye problems	-

The titles and abstracts of all identified records will be screened by two reviewers independently for potentially eligible studies. Potentially eligible studies will then be assessed in full-text for their eligibility independently by two reviewers. Any disagreement between reviewers will be resolved through consensus or consultation with a third reviewer. The Rayyan (https://www.rayyan.ai/) software will be used for the screening and study selection process. The screening and selection process of RCTs related to the clinical assessment will be summarized using a PRISMA flow diagram.

6.1.3 Data extraction

Data will be extracted into a predefined work sheet, which will be pilot-tested with selected studies retained after full-text screening.

For included studies on efficacy and safety, the following information will be extracted:

- Study characteristics (e.g., author, year of publication, study type, start and end of the study, simple size, follow-up time)
- Participant characteristics (e.g., age, sex, definition of early breast cancer adopted, prognostic factors)
- Intervention and comparator data (e.g., adjuvant/neoadjuvant, dose, frequency, treatment duration)

  [NB: to investigate the potential effects of concomitant cancer treatments information on chemotherapy type and duration will be extracted]
- Data on outcomes as defined in the PICO (e.g., OS, DFS, HRQoL, adverse effects, serious adverse effects)
- Information to assess the quality of studies (i.e., data necessary to assess risk of bias in RCTs according to the Cochrane standard)
- Information on the non-inferiority margin and on whether an intention-to-treat (ITT) or per-protocol (PP) analysis was done.

In case of missing information on DFS or OS, the authors of the studies will be contacted via email.

6.1.4 Risk of bias and GRADE assessment

Risk of bias in the included RCTs will be assessed using the Cochrane Risk of Bias (RoB) 2 tool.[35 36]

The following domains will be addressed:

- bias arising from the randomization process
- bias due to deviations from intended interventions
- bias due to missing outcome data
- bias in measurement of the outcome
- bias in selection of the reported result

These domains will be judged with ‘low risk of bias’, ‘some concerns’ or ‘high risk of bias’.

The certainty of evidence of selected patient-relevant outcomes will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[37–39]

The following prioritized outcomes will be considered:

- DFS
- OS
- HRQoL
- Adverse effects
- Serious adverse effects

In brief, the GRADE assessment will address different aspects including:

- Study limitations (risk of bias)
- Imprecision (when 95% CIs around the point estimate are wide and/or are close to null effect)
- Inconsistency (that is, differences in effect estimates across studies)
- Indirectness (that is, differences in patient characteristics, differing [co-] intervention, differing extent to which the intervention and/or comparator treatment is optimally conducted, and differences in measurement of outcomes)
- Dissemination bias (publication bias)

Based on these criteria, the certainty of the evidence for each outcome will be categorized as either high, moderate, low, or very low. The results will be presented in a Summary of Findings (SoF) Table.

Risk of bias assessment and the GRADE assessment will be conducted independently by two researchers. Any disagreements will be resolved by discussion and consensus involving, when needed, a third person.

6.1.5 Data synthesis

All statistical analyses will be conducted using R statistical software (v4.2.2 or higher).[40]

6.1.5.1 Measures of treatment effect

The intention is to conduct meta-analyses for all predefined outcomes. The realization of any given meta-analysis will depend on the availability of sufficient data from sufficiently homogenous studies in terms of clinical and methodological homogeneity. Effect estimates will be calculated based on a random effects model.[41]

The measure for OS and DFS will be the hazard ratio (HR) with its 95%-CI. A HR less than 1.0 favours ≤ 6 months regimens and a HR larger than 1.0 favours 12 months regimens.

The measure for combining toxicities or other adverse effects will be the risk ratio (RR) with its 95%-CI. A RR greater than 1.0 indicates that the ≤ 6 months treatment is more toxic (shows more adverse effects) than the 12 months treatment and a RR less than 1.0 suggests that the 12 months treatment is more toxic (shows more adverse effects) than the ≤ 6 months treatment.

Outcomes measured with a scale as continuous outcomes (e.g., HRQoL) will be analysed. The effect estimate for each continuous outcome will be expressed as the mean difference (MD) with its 95% CI. Where continuous outcomes are measured using different scales, the effect of the intervention will be expressed as the standardized mean difference (SMD) with its 95% CI.

6.1.5.2 Heterogeneity

Different types of heterogeneity (owing to different clinical characteristics, different study designs or small study effects) will be evaluated and statistically quantified based on I^2. Thereby, an $I^2 \geq 75$ % will be considered as considerable heterogeneity.[42]

Sensitivity analyses (considering the risk of bias) and predefined subgroup analyses (for different clinical characteristics including different populations, interventions, and comparators) will be performed irrespective of the presence of "significant" heterogeneity (see next section).

6.1.5.3 Subgroup analysis

Subgroup analyses will be performed to examine differences in effect estimates depending on:

- Characteristics of the population (prognostic factors that could possibly modify efficacy of different treatment durations (e.g., node-positive or negative status, positive or negative hormonal receptors, tumour size, age > 60 or < 60 years)).
- Characteristics of the intervention (less than 6 months, 6 months, modality of administration, neoadjuvant, adjuvant)
- Characteristics of the comparator
- Characteristics of the concomitant chemotherapy

Sensitivity analyses will be conducted to determine the impact of bias through the exclusion of studies with high risk of bias. In case of any differences between these estimates, these will be considered in the results and discussion.

6.1.5.4 Dealing with missing data

Data will be analysed, if possible, on an ITT and PP basis, according to recommendations for systematic reviewers for addressing missing data in clinical trials.[42] Trial register records will also be checked and authors may be contacted to obtain additional information on missing data (for the outcomes DFS and OS).

If statistical pooling is not appropriate, a narrative description will aim to synthesize the direction and size of any observed effects across studies in the absence of a meta-analysis.

6.1.5.5 Non-inferiority margin

A 6-month treatment duration or less compared to a 12 months treatment duration is not intended to provide superiority for efficacy outcomes (OS, DFS). Therefore, the aim is to assess if a shorter treatment duration is non-inferior and not "unacceptably worse" to the 12 months treatment by applying a non-inferiority margin as a decision threshold for efficacy outcomes.

The HTA will aim to investigate non-inferiority of ≤ 6 months versus 12 months of trastuzumab treatment for the outcomes of DFS and OS, and superiority of ≤ 6 months versus 12 months of treatment for all other outcomes (e.g., cardiotoxicity). The definition/selection of the non-inferiority margin to be used for the analyses in the efficacy domain requires additional considerations.

A decision based on superiority trials is different from a decision based on non-inferiority trials. A decision based on superiority trials aims to determine whether one intervention is superior to another.[43] A decision based on non-inferiority trials aims to determine whether one (typically new) intervention is not worse than a reference treatment (control) by more than a prespecified (non-inferiority) margin. Moreover, a decision based on an equivalence trial aims to determine whether one (typically new) intervention is therapeutically similar to another, usually an existing treatment.

The selection of a non-inferiority margin depends on what is deemed a clinically acceptable loss of efficacy for the benefits gained by de-escalation. It is inherently subjective and should be consensus-based.

According to a preliminary guidance document addressing equivalence and non-inferiority in the context of systematic reviews and meta-analyses there are several ways to select/define a non-inferiority margin:[44] (1) use a margin based on an already conducted study, (2) use a margin suggested by clinicians and experts based on experience and expert knowledge, or (3) use a margin based on statistical calculation.

In several non-inferiority analyses, the non-inferiority margin was selected/calculated based on purely statistical methods (e.g., using a mean/median of the non-inferiority margin used in included RCTs). However, it is also possible to select a non-inferiority margin based on the available RCTs and the opinions of clinicians and other important stakeholders such as patients.

A margin of up to 3% is often used in non-inferiority trials in oncology [45]. This non-inferiority margin was also *a priori* considered as acceptable by clinicians and patients in the planning phase of one of the primary studies of relevance for the present HTA, i.e. the PERSEPHONE trial.[46] Please note that the preliminary search revealed that the different primary studies of potential relevance for the present HTA

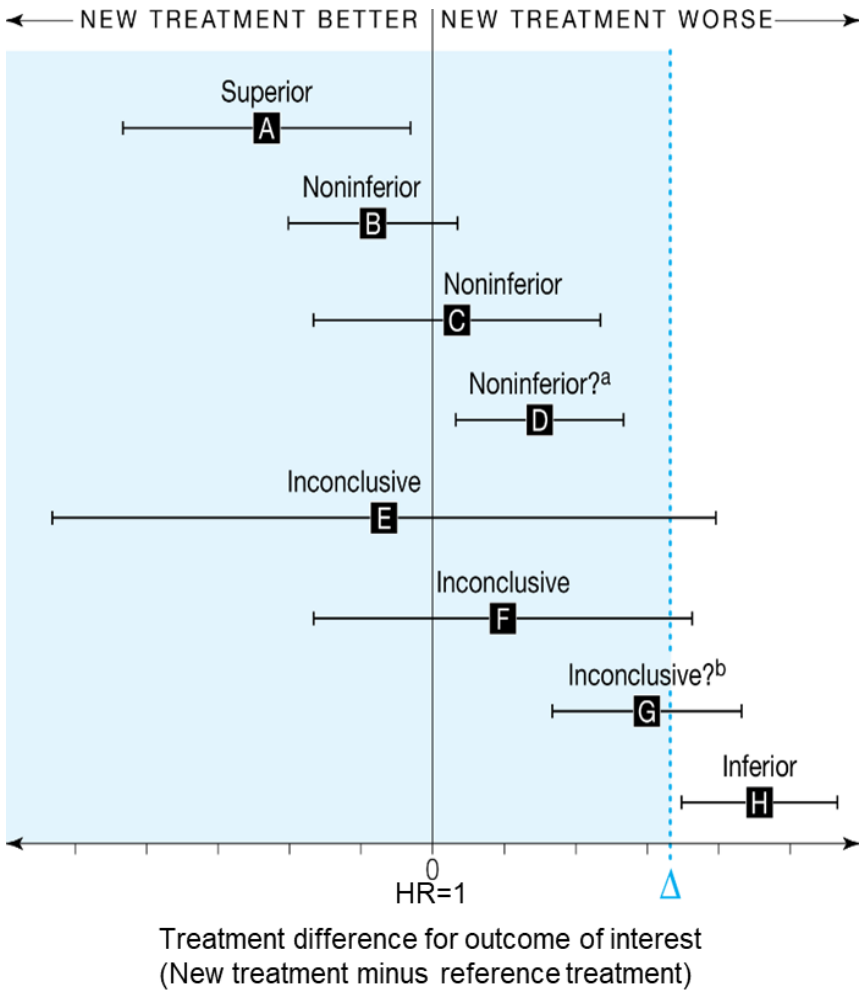
used different non-inferiority margins (with absolute risk differences ranging between 2% and 8% for DFS).[13 14 16–18 47]

After consultation with three Swiss clinicians with large expertise in this field of systemic breast cancer treatment (two oncologists and one gynaecologist), it has been decided that the above-mentioned non-inferiority margin (i.e., absolute risk difference of 3%) will be used in the planned HTA report for the efficacy outcomes DFS and OS.[46] Considering the clinical heterogeneity of non-inferiority margins, the potential impact of the non-inferiority margin will be investigated using lower (2% absolute risk difference) and higher (4% absolute risk difference) margins.

The results (HR) for OS and DFS will be classified as follows (adapted from Piaggio et al. 2012):[43]

a) The ≤ 6 months treatment is superior: the whole 95% CI lies to the left of HR = 1. (See situation A in Figure 1)
b) The ≤ 6 months treatment is non-inferior:
    - Non-inferior but not superior: the whole 95% CI lies to the left of the non-inferiority margin (Δ) and includes HR= 1 (i.e., includes no effect). (See situation B and C in Figure 1)
    - Formally non-inferior and factually (statistically) inferior: the whole 95% CI lies wholly to the left of the non-inferiority margin and wholly to the right of HR = 1. Inferiority factually exists in the sense that a null treatment effect (HR=1) is excluded. This circumstance is rare: it requires a very large sample size and can also result from a non-inferiority margin that is too wide. (See situation D in Figure 1). In this HTA, this scenario will be considered non-inferior.
c) The result regarding non-inferiority of the ≤ 6 months treatment is inconclusive:
    - The result regarding non-inferiority of the ≤ 6 months treatment is inconclusive, and the difference is non-significant: the 95% CI includes the non-inferiority margin and HR=1. (See situation E and F in Figure 1)
    - The result regarding non-inferiority of the ≤ 6 months treatment is inconclusive, but the difference is statistically significant: the 95% CI includes the non-inferiority margin and is wholly to the right of HR=1. This CI is inconclusive in that it is still plausible that the true treatment difference may be less than the non-inferiority margin, but the ≤ 6 months treatment is significantly worse than the reference treatment. (See situation G in Figure 1)
d) The ≤ 6 months treatment is inferior: the whole 95% CI is to the right of the non-inferiority margin. (See situation H in Figure 1)

Figure 1. Possible scenarios of observed treatment differences for outcomes of interest (e.g., harms) in non-inferiority trials (from Piaggio et al. 2012.[43])



Error bars indicate 2-sided 95% confidence intervals (CIs). The blue dashed line at x = Δ indicates the non-inferiority margin; the blue tinted region to the left of x = Δ indicates the zone of non-inferiority. A, If the CI lies wholly to the left of zero, the new treatment is superior. B and C, If the CI lies to the left of Δ and includes zero, the new treatment is non-inferior but not shown to be superior. D, If the CI lies wholly to the left of Δ and wholly to the right of zero, the new treatment is non-inferior in the sense already defined but also inferior in the sense that a null treatment difference is unlikely. This puzzling circumstance is rare, because it requires a very large sample size. It also can result from a non-inferiority margin that is too wide. E and F, If the CI includes Δ and zero, the difference is non-significant but the result regarding non-inferiority is inconclusive. G, If the CI includes Δ and is wholly to the right of zero, the difference is statistically significant, but the result is inconclusive regarding possible inferiority of magnitude Δ or worse (i.e., non-inferiority is not demonstrated). H, If the CI is wholly above Δ, the new treatment is inferior. [a] This CI indicates non-inferiority in the sense that it does not include Δ, but the new treatment is statistically significantly worse than the standard. Such a result is unlikely because it would require a very large sample size. In this HTA, this scenario will be considered non-inferior. [b] This CI is inconclusive in that it is still plausible that the true treatment difference is less than Δ, but the new treatment is significantly worse than the standard. Adapted from Piaggio et al.[43]

6.1.6 Quality control

Quality of the systematic review, meta-analysis, and synthesis of the clinical assessment will be ensured by conducting the study screening and selection, data extraction, risk of bias and GRADE assessment in duplicate and independently by two reviewers. A third reviewer will be involved in case of any uncertainties or disagreements between these reviewers. All findings will be circulated, checked for plausibility, and discussed among the whole assessment team and with the involved clinical experts.

6.2 Economic assessment

In this section, the approach to address the health economic research questions is described. In brief, it will consist of a systematic literature review of existing health economic evidence, the development of a *de novo* cost-effectiveness model, and a budget impact analysis (based on the results of the cost-effectiveness analysis).

6.2.1 Systematic review of the economic literature

6.2.1.1 Databases and search strategy

The systematic literature search for economic evaluations will be conducted in Medline, Embase, the International Network of Agencies for Health Technology Assessment (INAHTA) database, EconLit, and the National Health Service Economic Evaluation Database (NHSEED). The search strategy will be based on the clinical terms used in the clinical assessment part combined with specific economic search filters.

The search string will be obtained by integrating and combining the search string used in the clinical part and published search strings for health economic analyses.[48] Unspecific abbreviations such as CUA (for cost-utility analysis) or CBA (for cost-benefit analysis) will not be used.

6.2.1.2 Inclusion/exclusion criteria and study selection

Compared to the inclusion/exclusion criteria for the clinical assessment, the economic assessment will focus on other study designs (economic evaluations instead of RCTs) and economic outcomes (Table 2). The process of identification of economic studies will be graphically summarized using a PRISMA flow diagram.

Table 2 Study inclusion and exclusion criteria for the economic assessment.

Criterion	Inclusion	Exclusion
Publication period	No restriction.	-
Publication status	Published full text available.	Full text not available. Only conference abstract.
Language	English, German, French, Italian	-
Setting/Location	No restriction.	-
Study design	Health economic analysis, including within-trial or model-based cost minimization, cost-effectiveness, cost-utility, cost-benefit, and budget impact analyses	Not health economic analyses
Population	Females or males (≥18 years) with early breast cancer.	Females or males without breast cancer or with advanced breast cancer. Animal studies
Intervention	PICO 1: Adjuvant or neoadjuvant trastuzumab treatment, ≤ 6 months treatment duration. PICO 2: Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, ≤ 6 months treatment duration.	Other drugs for the treatment of early breast cancer.
Comparator	PICO 1: Adjuvant or neoadjuvant trastuzumab treatment, 12 months treatment duration. PICO 2: Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, 12 months treatment duration.	Other drugs for the treatment of early breast cancer. No drug treatment / placebo.
Outcomes	Cost-effectiveness Budget impact	-

As for the clinical assessment, studies will initially be title-and-abstract-screened by two reviewers independently, according to the inclusion/exclusion criteria. Two researchers will independently review full texts of studies retained from this phase for inclusion. Any disagreement will be resolved through consensus or consultation with a third reviewer.

6.2.1.3 Data extraction, analysis, and synthesis

One reviewer will extract data into a predefined work sheet, which will be pilot-tested with selected studies retained after full-text screening. Extracted data will be checked by a second reviewer. Any disagreement will be solved by consensus. Where consensus cannot be found, a third reviewer will be consulted.

Following data will be extracted:

- Type of economic evaluation

- Type of model used
- Country
- Study population
- Intervention
- Comparator(s)
- Perspective of cost assessment (e.g., healthcare, societal)
- Cost types included
- Time horizon and discount rate
- Clinical and HRQoL-related data sources and assumptions used as input parameters
- Cost, life year, and quality adjusted life year (QALY) results per strategy (including currency and cost year)
- Incremental cost-effectiveness ratio (ICER) or equivalent
- Information to assess the quality of studies and reporting
- Conflicts of interest and funding sources

The quality of reporting of economic studies will be assessed according to Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022).[49] However, the assessment will be restricted to a smaller set of key items, like for example:

- Item 5: study population (Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).
- Item 7: comparators (Describe the interventions or strategies being compared and why chosen).
- Item 8: perspective (State the perspective(s) adopted by the study and why chosen).
- Item 9: time horizon (State the time horizon for the study and why appropriate).
- Item 23: Summary of main results (Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure).

The selected items are considered fundamental as they confirm that the population, intervention, and comparator in the identified cost-effectiveness analysis are in line with the PICO of this HTA.

Details on the cost-effectiveness studies will be summarized in tabular and/or graphical form. Results may presumably be divided according to treatment duration (≤ 6 versus 12 months; 6 versus 12 months; <6 versus 12 months).

6.2.2 Cost-effectiveness analysis

In a preliminary search for economic analyses in Medline, only a moderate number of publications has been identified.[50–56] Four studies investigated the cost-effectiveness of 6 months of adjuvant trastuzumab versus 12 months of adjuvant trastuzumab for non-metastatic/early breast cancer,[50 52–54] while four studies investigated even shorter durations of trastuzumab treatment (versus 12 months).[51 54–56] While all RCTs providing clinical outcomes identified in the preliminary search were conducted in countries with healthcare settings comparable to Switzerland, many of the available economic evaluations were conducted in countries that are generally considered less comparable (Egypt, India, Iran).

Although a numerical adaptation of the cost results of the identified studies to Switzerland is technically possible, such a “simple” adaptation would not be the most appropriate approach in the present case, given these circumstances.

If the findings of the systematic search will confirm the findings of the preliminary search, a *de novo*, model-based cost-effectiveness analysis for Switzerland will be planned. The approach will be informed by the results of the economic literature search, the results of the clinical assessment and inputs from additional sources of data and information (including Swiss tariff systems and clinical expert information on Swiss practice).

Ideally, a model for both PICOs should be created. However, according to the preliminary literature searches, it can be anticipated that it is unlikely that enough information to conduct a cost-effectiveness analysis for PICO 2 will be identified.

If the available data allow, analyses of several subgroups will be planned: for example, supgroup analyses by age (above/below 60 years), estrogen receptor status, nodal status, disease stage, timing of administration (sequential, concomitant), or risk of cardiovascular problems may be considered.

6.2.2.1 Structure of the model

For this project the probably best approach will be to aim to replicate and adapt an existing model that is well described. The *de novo* cost-effectiveness analysis will be conducted for Switzerland based on the PICO. To avoid inefficient complication of the model, the population modelled will be limited to women with early breast cancer. The treatment duration in the intervention group will be 6 months (versus 12 months in the comparator group).

The *de novo* model will be most likely a four-health state Markov model, with states representing DFS, locoregional recurrence, distant metastasis, and death. The structure of the model will be discussed with clinical experts to ensure it reflects daily clinical practices in Switzerland.

6.2.2.2 Perspective

The cost-effectiveness analysis will be performed from a healthcare payer perspective. The costs of healthcare services covered by the Swiss mandatory health insurance will be analysed, irrespective of the actual payer (mandatory health insurance, other social insurance, government, out-of-pocket). The analysis will not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

6.2.2.3 Time horizon

The time horizon for the cost-effectiveness analysis needs to be long enough to capture the clinical and economic differences arising from the different treatment options. Therefore, a lifetime horizon is to be expected. Alternative time horizons (e.g., 5, 10, or 15 years) will eventually be explored as part of the scenario analyses.

6.2.2.4 Discounting

Costs and utilities will be discounted at an annual rate of 3%. Additionally, discount rates of 0% and 5% will be explored in the univariate analysis.

6.2.2.5 Uncertainty

In order to investigate parameter and structural uncertainty, one-way sensitivity analyses, probabilistic sensitivity analyses, and several scenario analyses will be performed. The selection of sensitivity and scenario analyses to be performed will depend on intermediate results.

If possible, costs and cost-effectiveness of biosimilars to Herceptin® approved after 2019 (e.g., Herzuma®, Kanjinti®, Ogivri®, Trazimera®) will be also investigated.[2]

Only public prices for trastuzumab and pertuzumab will be considered. Regarding the combined treatment of pertzumab and trastuzumab, the pharmaceutical companies have a commercial arrangement with the FOPH. This makes pertuzumab and trastuzumab available to the health system with a price discount when given in combination (www.spezialitätenliste.ch). Confidential and therefore to the public unknown price discounts will be explored in scenario analyses.

6.2.2.6 Model input parameters and data sources

It is planned to obtain information required for the economic analysis through:

- The results of the clinical part of the assessment.
- The results of the systematic health economic literature review.

- Input from Swiss clinical experts.
- The National Institute for Cancer Epidemiology and Registration (NICER)
- The Swiss Federal Statistical Office (e.g., Swiss life table)
- The Swiss specialty list for drug prices (www.spezialitätenliste.ch).
- Swiss Hospital Statistics: patients with breast cancer will be identified through relevant treatments (e.g., CHOP codes), diagnostic codes (i.e., ICD-10 codes), and hospitalization codes (i.e., SwissDRG codes).
- Diagnosis Related Group case weights (SwissDRG online definition handbook 11.0 or a newer available version) for inpatient hospital costs.
- Swiss tariff framework for ambulatory and outpatient care (TARMED).
- Swiss BAG “Analysenliste” for laboratory costs.
- Additional exploratory searches, complemented with hand-searches of the grey literature and the world wide web (non-systematic) in order to identify manuscripts for event rates, health resource use and costs that are not available from the above-mentioned sources.

A more detailed description of the health economic analysis will be developed during the health economic analysis plan and described in the final HTA report.

6.2.3 Budget impact analysis

The results of the cost-effectiveness analysis will be used as basis for a budget impact analysis. Swiss epidemiological data on early breast cancer incidence will be combined with the estimated cost difference between the intervention and comparator strategies to estimate the yearly budget impact of switching from 12 months trastuzumab treatment to a shorter treatment duration.

6.2.3.1 Perspective

The budget impact analysis will be performed from a healthcare payer perspective. The costs of healthcare services covered by the Swiss mandatory health insurance will be analysed, irrespective of the actual payer (mandatory health insurance, other social insurance, government, out-of-pocket). The analysis will not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

6.2.3.2 Number of eligible patients

The population for budget impact analysis will consist of newly diagnosed early breast cancer patients.

6.2.3.3 Time horizon

The budget impact analysis will be estimated over a period of 5 years (from 2023 to 2027).

6.2.3.4 Discounting

For the budget impact analysis, a discount rate will not be applied (in line with standard health economic evaluation practice).

6.2.3.5 Uncertainty

Deterministic sensitivity and scenario analyses will be conducted to investigate which input parameter (e.g., estimated number of cases, treatment costs) have the highest impact on the estimated budget impact, and to estimate the impact of alternative assumptions.

If possible, the potential budget impact of biosimilars to Herceptin® approved after 2019 (e.g., Herzuma®, Kanjinti®, Ogivri®, Trazimera®) will be also investigated.[2]

In accordance with the cost-effectiveness analysis, public prices for trastuzumab and pertuzumab will be considered in primary analyses and confidential and therefore to the public unknown price discounts will be explored in scenario analyses.

6.2.4 Quality control

During the study selection process studies will be title-and-abstract-screened by two independent researchers according to the inclusion/exclusion criteria. Two researchers will independently review full texts of studies retained from this phase for inclusion. Any disagreement will be resolved through consensus or consultation with a third researcher.

During the data extraction process the data will be checked by a second researcher. Any disagreement will be solved by consensus. Where consensus cannot be found, a third researcher will be consulted.

Validation of the cost-effectiveness analysis, based for example on the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool, will be considered during the development of the model.[57]

6.3 Ethical, legal, social, and organizational assessment

6.3.1 Databases and search strategy

To address ethical, legal, social, and organizational (ELSO) issues, an exploratory literature search in Medline will be conducted. The search will be based on the clinical search terms used in the clinical assessment, combined with following search strings:

- *Ethical, social, legal items*: ("Ethical Analysis"[Mesh] OR "Legislation, Drug"[Mesh] OR "Social Change"[Mesh] OR (ethics[Title/Abstract] OR legal[Title/Abstract] OR law[Title/Abstract] OR social[Title/Abstract]))
- *Organizational items*: ("Organization and Administration"[Mesh] OR "Policy"[Mesh] OR "Insurance, Health"[Mesh] OR "Insurance Coverage"[Mesh] OR "Drug Approval"[Mesh] OR "Health Services Accessibility"[Mesh] OR (organization[Title/Abstract] OR policy[Title/Abstract] OR approval[Title/Abstract] OR coverage[Title/Abstract] OR regulation[Title/Abstract] OR regulatory[Title/Abstract] OR reimburse*[Title/Abstract] OR access[Title/Abstract] OR disinvestment[Title/Abstract] OR “drug dispensing”[Title/Abstract]))

6.3.2 Inclusion/exclusion criteria and study selection

Inclusion and exclusion criteria will be based on those of the clinical and health economic searches (see Table 1 and Table 2). However, impose no study design restrictions will be imposed as discussions of ELSO outcomes are expected to be presented in a variety of study designs.

6.3.3 Data extraction, analysis, and synthesis

A single researcher will screen and review the literature and identify studies relevant to the ELSO domains. The quality of evidence for ELSO outcomes will not be formally assessed. The main ELSO aspects identified through the exploratory search will be reported in a descriptive manner. This review will not be systematic. This is considered an appropriate approach as the primary purpose is to identify key aspects relevant to ELSO outcomes but not to provide an exhaustive or systematic review of the literature on these domains.

To the extent possible, possible issues related to short versus longer treatment duration will be compared to similar issues affecting other cancer treatments. The ethical, legal, and social issues (ELSI) checklist developed by the EUnetHTA will serve as basis for the ethical, legal, and social assessment.[58]

6.3.4 Quality control

In contrast to the clinical and economic assessments, and considering the exploratory nature of the literature search, a specific quality control is not planned. Nevertheless, the chapters concerning the ESLO outcomes will be reviewed by the clinical experts that have been recruited for this HTA.

7 Summary and Outlook

Summary

To summarize, for the clinical assessment, a systematic literature search will be conducted. Eligible studies will be randomised controlled trials (RCTs), that compared the treatment duration of 6 months or less of trastuzumab or trastuzumab combined with pertuzumab with a 12 months treatment in HER2-positive early breast cancer. Data extraction will include study and participant characteristics, intervention and comparator data, outcomes data. The risk of bias of the included RCTs will be assessed using the Cochrane RoB 2 tool, while the certainty of evidence will be assessed using GRADE. In the meta-analyses it is planned to investigate non-inferiority of ≤ 6 versus 12 months treatment for the outcomes DFS and OS, and superiority of ≤ 6 months versus 12 months treatment for all other relevant outcomes (e.g., cardiotoxicity). After consultation with clinical experts, it has been decided that as non-inferiority margin for the efficacy outcomes of DFS and OS, an absolute risk difference of 3% will be considered.

The economic assessment will consist of a systematic literature search of existing health economic evidence, the development of a *de novo,* model-based cost-effectiveness analysis for Switzerland, and a budget impact analysis.

To address ethical, legal, social, and organizational issues between the different treatment durations, an exploratory literature search will be conducted. The main issues identified will be reported in a descriptive manner.

Major challenges of this project include the availability of detailed information in the published RCTs (e.g., information on specific subgroups) and the development of the cost-effectiveness model. It is also not yet clear whether it will be possible to distinguish between adjuvant and neoadjuvant treatment since the RCTs identified so far are mainly concerned with adjuvant treatment.

Outlook

The HTA protocol is followed by the production of an HTA report based thereupon. The objective of the HTA report is to generate a focused assessment of various aspects of the health technology in question. The applied analytic methods, their execution and the results are described. The analytical process is comparative, systematic, and transparent. The external review group that was consulted during the protocol phase will be consulted again during the HTA phase. Subsequently the HTA draft report is presented to the stakeholders for consultation. Communication with the reviewers and the stakeholders is coordinated by the FOPH.

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9 Appendices

9.1 Search Strategies

MEDLINE (accessed via Ovid)

1	exp Breast Neoplasms/
2	((breast* or mamma*) adj4 (cancer* or neoplasm* or malignanc* or tumor* or tumour* or carcinoma* or adenocarcinoma*)).ti,ab.
3	1 or 2
4	exp Chemotherapy, Adjuvant/ or exp Neoadjuvant Therapy/
5	(adjuvant or neoadjuvant).ti,ab.
6	4 or 5
7	exp Trastuzumab/ or (trastuzumab or herceptin).ti,ab.
8	(duration or timing or time or short* or long* or course* or cycle* or length or ((compar* or difference or versus or vs*) adj4 (year* or month* or week* or day*))).ti,ab.
9	7 and 8
10	(pertuzumab or perjeta).ti,ab.
11	9 or 10
12	Clinical Trials as Topic/ or (randomized controlled trial or controlled clinical trial).pt. or (randomi?ed or randomly).ab. or (trial).ti.
13	exp Animals/ not Humans/
14	12 not 13
15	3 and 6 and 11 and 14

EMBASE (accessed via Elsevier)

#1	'breast cancer'/exp
#2	((breast* OR mamma*) NEAR/4 (cancer* OR neoplasm* OR malignanc* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma*)):ti,ab
#3	#1 OR #2
#4	'adjuvant chemotherapy'/exp OR 'neoadjuvant chemotherapy'/exp
#5	(adjuvant or neoadjuvant):ti,ab
#6	#4 OR #5
#7	'trastuzumab'/exp OR (trastuzumab or herceptin):ti,ab
#8	(duration OR timing OR time OR short* OR long* OR course* OR cycle* OR length OR ((compar* OR difference OR versus OR vs*) NEAR/4 (year* OR month* OR week* OR day*))):ti,ab
#9	#7 AND #8
#10	'pertuzumab'/exp OR (pertuzumab or perjeta):ti,ab
#11	#9 OR #10
#12	'clinical trial'/exp OR ('randomized controlled trial' OR 'controlled clinical trial'):it OR (randomi?ed OR randomly):ab OR (trial):ti
#13	'animals'/exp NOT 'humans'/exp
#14	#12 NOT #13
#15	#3 AND #6 AND #11 AND #14

CENTRAL (accessed via the Cochrane Library)

#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	((breast* OR mamma*) NEAR/4 (cancer* OR neoplasm* OR malignanc* OR tumor* OR tumour* OR

	carcinoma* OR adenocarcinoma*))
#3	#1 OR #2
#4	MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees
#5	MeSH descriptor: [Neoadjuvant Therapy] explode all trees
#6	(adjuvant or neoadjuvant)
#7	#4 OR #5 OR #6
#8	MeSH descriptor: [Trastuzumab] explode all trees
#9	(trastuzumab or herceptin)
#10	duration OR timing OR time OR short* OR long* OR course* OR cycle* OR length OR ((compar* OR difference OR versus OR vs*) NEAR/4 (year* OR month* OR week* OR day*))
#11	(#8 OR #9) AND #10
#12	(pertuzumab or perjeta)
#13	#11 OR #12
#14	#3 AND #7 AND #13