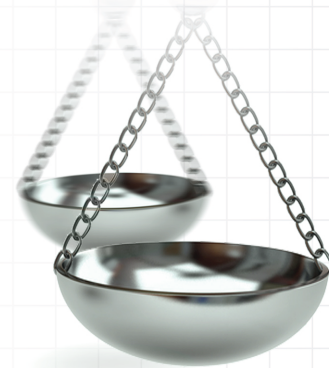




Costs of subcutaneous and intravenous administration of trastuzumab for patients with HER2-positive breast cancer

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Aim: Trastuzumab is available in an intravenous (iv.) and a subcutaneous (sc.) formulation. The objective of this study was to estimate the costs of administration of iv. and sc. trastuzumab treatment. **Materials & methods:** Via interviews, we identified all the activities associated with iv. and sc. administration. The outcome was time estimates. To estimate the administration costs, the time estimates were valued by average gross wages. **Results:** The iv. administration takes longer time as infusion time is longer (25 or 85 min). The iv. administration is associated with higher cost for 17 cycles; €971 (€1858 vs €887). **Conclusion:** sc. administration is associated with lower administration costs. Switching patients from iv. to sc. would make it possible to treat more patients without increasing the personnel resources.

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Research into cancer treatment continues with the aim of improving outcomes. New, innovative medicines (e.g., biologics) have bettered the prognosis as improved overall survival and improved progression free survival are experienced for many cancer patients [1].

Most oncology medicines are administered intravenously (iv.). However, some therapies can also be administered subcutaneously (sc.) which is more convenient and faster. Healthcare resources, as well as other resources associated with the patients, are limited, among others, implying a continuous focus on efficient treatment modes and monitoring. If possible, intuitively sc. administration should be preferred to iv. administration as sc. administration is faster and requires fewer resources.

Trastuzumab (Herceptin[®]) is available in an iv. formulation and an sc. formulation. Trastuzumab, as monotherapy or in combination with paclitaxel, docetaxel or carboplatin, is indicated for treatment of patients with HER2-positive breast cancer [2].

Trastuzumab is given every 3 weeks as neoadjuvant (prior to surgery) and adjuvant (after surgery) to patients with early breast cancer and as palliative treatment for patients with metastatic breast cancer. One year of trastuzumab treatment is the standard of care in the adjuvant setting, and the adjuvant setting is the focus of the comparison in manuscript.

Clinical trials have proven that the treatment effect and safety of trastuzumab is the same for iv. and sc. administration [3,4]. For the iv. formulation, infusion time is 90 min the first time and 30 min in the subsequent cycles. Injection time for the sc. formulation is 2–5 min [2]. In addition, the sc. formulation does not require drug preparation (fixed dose of 600 mg) apart from syringe preparation.

In Denmark, breast cancer is the most frequent cancer for women, and approximately 4800 are diagnosed every year [1]. Approximately 13% of all cases are HER2-positive [5]. Both administration forms, iv. and sc., are used in Denmark, but the trastuzumab administration practice and organization vary between oncology departments.

On average, the drug costs of the iv. (dose depending on body weight) and sc. (fixed dose) formulation are the same implying that knowledge about nondrug cost levels (i.e., administration costs) may be important in ensuring an efficient treatment mode.

It was the objective of this study to estimate the costs of the administration of iv. and sc. trastuzumab treatment, respectively, for patients with HER2-positive breast cancer from a healthcare and patient perspective.

Methods

Data on resource use

In Denmark, 12 oncology departments are treating HER2-positive breast cancer patients. Seven departments are located at regional hospitals and five at university hospitals. Data input on resource use were based on interviews in oncology departments with medical specialists and nurses and at hospital pharmacies with pharmacists and laboratory technicians.

Initially, we listed all the patient-related activities and tasks associated with the iv. and sc. administration of trastuzumab, respectively. Based on this list, we drafted an interview guide including questions covering all activities, tasks and time consumption associated with these activities and tasks. The interview guide also included questions regarding the usage of utensils related to iv. and sc. administration, respectively.

We pilot tested this interview guide at the department of oncology at Rigshospitalet in Copenhagen where we interviewed a nurse with comprehensive experience with trastuzumab treatment.

Based on this pilot interview, we adjusted the interview guide and subsequently additional interviews were performed in other oncology departments and at hospital pharmacies. The interviews at the pharmacies had a different focus as these interviews concentrated on the resources used at the pharmacies related to the preparation of trastuzumab (iv. and sc., respectively).

Costs

The main outcome of the interviews was estimates of the time consumptions associated with the specific patient-related activities and tasks in the oncology departments and at hospital pharmacies, respectively. The interviewees' information about estimates of time consumption (including minimum and maximum estimates) was organized in input tables categorized by activity and profession (medical specialist, nurse, secretary, pharmacist and laboratory technician).

To estimate the administration costs, the time estimates for the specific activities, categorized by profession, were assessed in hours, and these time estimates were valued by national, average, hourly gross wages including payroll tax for each profession (Table 2).

As different departments participated in the study, the time estimates were assessed as a weighted average (weighted based on the number of patients in treatment).

Similar to other studies and Danish guidelines, an overhead percentage on 100% for all wages was applied [8,9]. The overhead costs are included to take costs that are not directly related to labor or patient related activities (e.g., administrative costs or training/education costs) into account.

Patients' time was valued by applying national weighted unit costs for working and leisure time (Table 2) [7] assuming that some patients work whereas others are outside the workforce. Patients' time included the time spent at the hospital department (i.e., from arrival till leaving) whereas transportation time and possible time for accompanying relative is not included.

iv. administration's extra use of utensils was estimated on the basis of information from the hospital pharmacies and a previous Danish study [8].

Instead of a peripheral vein catheter (venflon), some iv. patients have a permanent port (port-a-cath). National tariffs for implanting the permanent port were applied to a unit cost estimate for this procedure [10].

Both iv. and sc. patients occupy the department's waiting/observation rooms and treatment rooms when they are treated and subsequently observed. In estimating the cost of utilization of the department rooms, we applied a standard cost per square meter per hour estimated in a previously published Danish study (Table 2) [8].

Results were estimated from a healthcare (hospital) perspective. In addition, the costs of the patients' time were included, that is, the administration costs are presented with and without the inclusion of the costs of the patients' time.

Table 1. Time consumption per cycle, subcutaneous and intravenous.

Personnel	Mean time consumption (min)	Minimum time consumption (min)	Maximum time consumption (min)
sc.			
Secretary	1	1	3
Nurse	16	13	21
Medical specialist	2	1	3
Pharmacist	3	2	4
Laboratory technician	9	8	10
Hospital porter	5	2	8
Patient:			
Direct contact with nurse	13	10	19
Waiting time	0	0	0
Observation time:			
– First cycle	360	360	360
– Second cycle	93	93	94
– Third cycle	66	66	66
– Subsequent cycles	0	0	0
iv.			
Secretary	1	1	3
Nurse:			
– First cycle	66	62	72
– Second cycle	36	32	42
– Third cycle	36	32	42
– Subsequent cycles	26	22	30
Medical specialist	1	1	1
Pharmacist	3	2	4
Laboratory technician	22	21	23.5
Hospital porter	5	2	8
Patient			
Direct contact with nurse:			
– First cycle	111	106	117
– Second cycle	51	46	57
– Third cycle	51	46	57
– Subsequent cycles	31	27	36
Waiting time	4	3	4
Observation time:			
– First cycle	360	360	360
– Second cycle	61	61	61
– Third cycle	56	56	57
– Subsequent cycles	1	1	1

iv.: Intravenous; sc.: Subcutaneous.

Univariate sensitivity analyses were performed by presenting the range in the administration costs by applying the minimum and maximum estimates for time consumption related to the specific activities and by lowering the applied overhead percentage.

Finally, for iv. and sc., respectively, results are presented as the total cost of administration for 17 cycles (corresponding to 1-year treatment) and as the costs for the first, second and third cycle and subsequent cycles.

Results

Interviews were performed in five oncology departments, three departments located at a university hospital and two departments located at a regional hospital. This corresponds to 42% of all oncology departments involved in treatment of HER2-positive breast cancer. The participating departments can be considered geographically

Table 2. Applied unit costs.				
Profession	Hourly gross wages (incl. overhead), €	Source		
Secretary	70	Estimated based on yearly wages [6]		
Nurse	82	Estimated based on yearly wages [6]		
Medical specialist	191	Estimated based on yearly wages [6]		
Pharmacist	74	Estimated based on yearly wages [6]		
Laboratory technician	103	Estimated based on yearly wages [6]		
Hospital porter	67	Estimated based on yearly wages [6]		
	Cost per hour, €	Source		
Patient's time	15	[7]		
Utilization of department rooms	Cost per hour, €	Min, €	Max, €	Source
Treatment room, iv.	3.3	2.8	3.5	[8]
Treatment room, sc.	2.1	1.9	2.4	[8]
Observation/waiting room	1.3	0.9	1.7	[8]
2017 price level.				
Incl.: Including; iv.: Intravenous; Max: Maximum; Min: Minimum; sc.: Subcutaneous.				

representative as four out of five hospital regions are represented in the interviews. At three departments, oncologists and nurses participated in the interview and at two departments only nurses participated. In total, three oncologists and five nurses were interviewed.

In addition, we performed interviews with pharmacists and laboratory technicians at two hospital pharmacies, one at a pharmacy located at a university hospital and one at a regional hospital.

Figure 1 provides an overview of the activities and tasks for iv. and sc. administration, respectively, that were identified via the interviews. The iv. administration takes longer time as infusion time is 90 min at the first cycle and 30 min at subsequent cycles whereas the injection time is 2–5 min at all sc. cycles. In addition, there may be extra waiting time for iv. patients as some departments do not order trastuzumab until the iv. patient has arrived at the department.

The average time estimates for the activities categorized by personnel appear in Table 1. Compared with sc. administration, it is seen that the time consumption for nurses and laboratory technicians and the patients' time consumption is markedly higher for iv. administration. This results from the fact that the infusion time for iv. patients is markedly longer than the injection time for sc. patients and that preparation of the infusion fluid at the hospital pharmacy also takes a longer time than preparation of the sc. syringe. However, for iv. administration the nurse is on average treating two patients simultaneously. As more iv. patients are treated in the same room the nurse can initiate two to four treatments within an hour.

According to guidelines, patients treated with trastuzumab should be observed by a healthcare professional after the infusion or injection. All patients regardless of administration form are observed 6 h (360 min) after the first cycle. For the second, third and fourth cycle, observation times are shorter and there is variation in practice. After the fourth cycle, the patients are no longer observed.

Applying the results from Table 1 and the unit cost estimates (Table 2), the total administration costs for 17 cycles (corresponding to approximately 1 year) for sc. and iv., respectively, are shown in Figure 2, and the administration costs per cycle (i.e., first, second, third and subsequent cycles) for sc. and iv., respectively, appear in Table 3.

Excluding the patient's time consumption, iv. administration is associated with higher cost for 17 cycles; €971 (i.e., €1858 vs €887 cf.; Figure 2). Inclusion of the patient's time consumption increases the extra costs associated with iv. administration from €971 to €1085 (i.e., €2159 vs €1074).

From Table 3, it is seen that all sc. cycles are associated with higher costs and especially the administration costs for the first cycle are high (€171 vs €60, excluding patient's time). Excluding patient's time consumption, the extra administration costs are €111 for the first cycle, €66 for the second cycle, €67 for the third cycle and €51 for subsequent sc. cycles. Including patient's time consumption, the extra administration costs are €137 for the first, €69 for the second, €74 for the third and €57 for subsequent sc. cycles.

Finally, in Table 4, as a univariate sensitivity analysis, the range in the cost estimates is shown. Lowering the overhead percentage from 100 to 50% or applying the minimum time estimates, iv. administration is still associated

Table 3. Administration costs per cycle, subcutaneous and intravenous.

	1st cycle, €	2nd cycle, €	3rd cycle, €	Subsequent cycles, €
sc.				
Personnel				
Secretary	1.4	1.4	1.4	1.4
Nurse	22.4	22.4	22.4	22.4
Medical specialist	5.5	5.5	5.5	5.5
Pharmacist	5.1	5.1	5.1	5.1
Laboratory technician	11.1	11.1	11.1	11.1
Hospital porter	5.6	5.6	5.6	5.6
Other costs				
Treatment room	0.5	0.5	0.5	0.5
Observation/waiting room	8.0	2.1	1.5	0.0
Patient's time				
Direct contact with HCP	3.3	3.3	3.3	3.3
Waiting time	0.0	0.0	0.0	0.0
Observation time	90.4	23.4	16.5	0.0
Total cost, excl. patient's time	60	54	53	52
Total cost, incl. patient's time	153	80	73	55
iv.				
Personnel				
Secretary	1.7	1.7	1.7	1.7
Nurse	90.2	49.3	49.3	35.5
Medical specialist	4.0	4.0	4.0	4.0
Pharmacist	5.1	5.1	5.1	5.1
Laboratory technician	27.3	27.3	27.3	27.3
Hospital porter	5.6	5.6	5.6	5.6
Other costs				
Treatment room	6.1	2.8	2.8	1.7
Observation/waiting room	8.1	1.4	1.3	0.1
Utensils	8.4	8.4	8.4	8.4
Port-a-cath	14.0	14.0	14.0	14.0
Patient's time				
Direct contact with HCP	27.8	12.7	12.7	7.7
Waiting time	0.9	0.9	0.9	0.9
Observation time	90.4	15.3	14.1	0.3
Total cost, excl. patient's time	171	120	120	103
Total cost, incl. patient's time	290	149	147	112
2017 price level. excl.: Excluding; HCP: Healthcare professional; incl.: Including; iv.: Intravenous; sc.: Subcutaneous.				

Table 4. Administration costs for 17 cycles: range, subcutaneous and intravenous.

Administration costs	Average, €	Average: 50% OH, €	Min, €	Max, €
Total adm. cost, incl. patient's time, sc.	1074	857	790	1428
Total adm. cost, incl. patient's time, iv.	2159	1802	1912	2444
2017 price level. adm.: Administration; incl.: Including; iv.: Intravenous; Max: Maximum; Min: Minimum; OH: Overhead; sc.: Subcutaneous.				

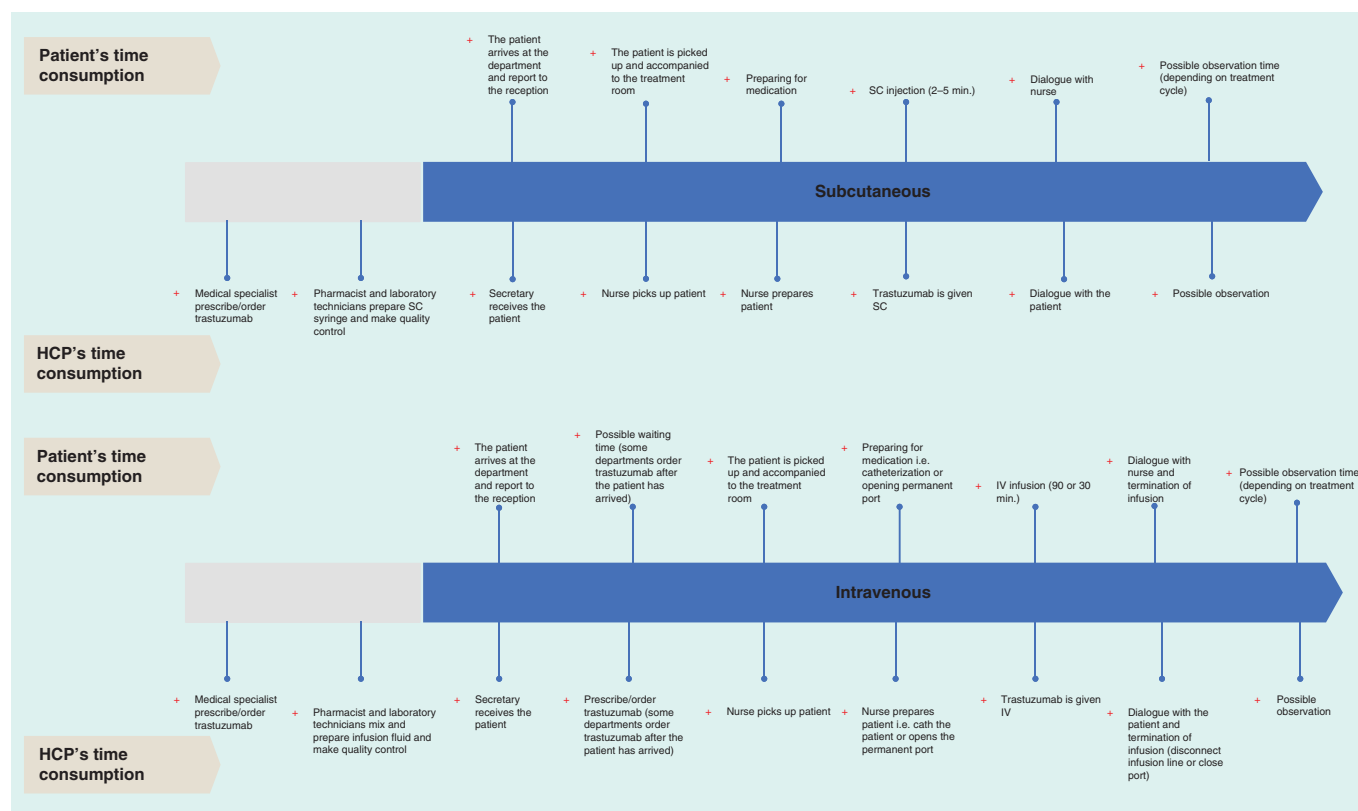


Figure 1. Activities.

HCP: Healthcare professional; IV: Intravenous; SC: Subcutaneous.

with higher costs. Including patient's time, the extra cost for iv. administration compared with sc. administration ranges from €945 to €1122, when minimum estimates for sc. and iv. and maximum estimates for sc. and iv. are compared. However, when minimum time estimates for iv. and maximum time estimates for sc. are compared, the extra cost of iv. treatment is estimated to €484. Similarly, when maximum time estimates for iv. and minimum time estimates for sc. are compared, the extra cost of iv. treatment is estimated to €1654.

As stated, the drug costs of the iv. and sc. formulation are on average the same and the hospital pharmacies report that there is no drug waste associated with iv. administration. That is, drug wastage is limited as several trastuzumab patients (iv.) are treated the same day. However, in real life it can be difficult to dose precisely according to patients' weight and there can be wastage if vials do not equal the exact amounts of patients regarding iv. treatment.

Discussion

This study estimated the administration costs for iv. and sc. treatment, respectively, of HER2-positive breast cancer patients. The results show that sc. compared with iv. trastuzumab treatment primarily saves nurse, laboratory technician and patient time and results in cost savings for the first and subsequent treatment cycles. Depending on the assumptions and applied time estimates, the extra cost of administration associated with iv. is approximately €1000 for 17 cycles corresponding to 1-year treatment.

Costs of patient's time must be considered as a conservative estimate as transportation time is not included.

The cost of implanting of a permanent port in some patients was included. As this port may be used for other iv. treatments as well, a 100% inclusion of these costs may constitute an overestimate.

Our results are similar to another Danish study reporting the costs of iv. and sc. administration in biologic treatment of patients with inflammatory bowel disease [11] as well as the results are confirmed by other studies analyzing sc. and iv. administration of trastuzumab [12–14].

Our analysis is based on interviews and not an observational; time and motion study assuming the latter would generate more precise time consumption estimates. However, the reported time estimates from the interviewed

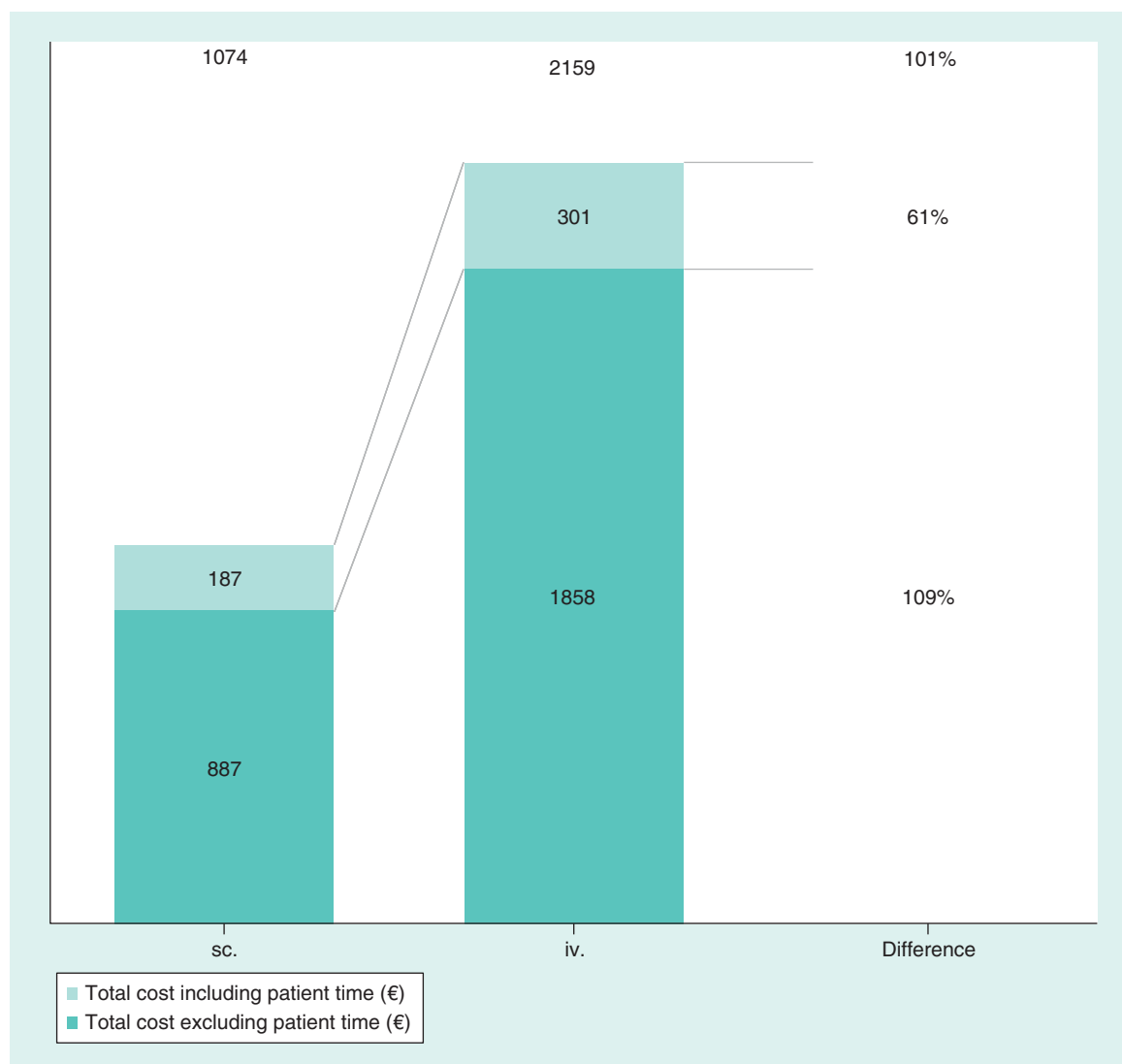


Figure 2. Total administration costs for 17 cycles sc. and iv., respectively (€, 2017 price level).

IV: Intravenous; SC: Subcutaneous.

participants for the specific activities are quite consistent, indicating that the estimates are consistent and that observations probably would not change the time estimates notably.

In addition to being cost saving, it should also be noted that sc. administration, compared with iv., is preferred by most patients if given the option. This is documented in a Swedish study and in the PrefHER study [13,15]. Furthermore, the safety profile of sc. trastuzumab is consistent with the known safety profile of iv. treatment in early breast cancer.

This study focuses on the administration cost. However, in addition to increased administration cost, iv. treatment may also lead to drug wastage (due to dose depending on body weight). However, laboratory technicians and pharmacists report that drug wastage is minimized as infusion fluid for more patients are prepared the same day, implying that surplus from one patient is used for another patient. Other studies do report that the drug wastage may be considerable [16].

Conclusion

As sc. administration is associated with lower administration costs, this implies that switching patients from iv. to sc. would make it possible to treat more patients without increasing the personnel resources.

Summary points

- Interviews were performed in five oncology departments, three departments located at a university hospital and two departments located at a regional hospital corresponding to 42% of all oncology departments involved in treatment of HER2-positive breast cancer.
- Subcutaneous (sc.) compared with intravenous (iv.) trastuzumab treatment primarily saves nurse, laboratory technician and patient time and results in cost savings for the first and subsequent treatment cycles.
- The safety profile of sc. trastuzumab is consistent with the safety profile of iv. treatment.
- sc. administration, compared with iv., is preferred by most patients if given the option.
- sc. administration is associated with lower administration costs, implying that switching patients from iv. to sc. would make it possible to treat more patients without increasing the personnel resources.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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