A Systematic Review of Time and Resource Use Costs of Subcutaneous Versus Intravenous Administration of Oncology Biologics in a Hospital Setting

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Abstract

Background The introduction of human epidermal growth factor receptor 2 (HER2)-targeted treatment options, including dual HER2 blockade, has improved the prognosis for patients with HER2-positive breast cancer (BC) substantially. However, most of these treatments are administered via the intravenous (IV) route, which can present many challenges, such as long infusion and observation times, issues associated with repeated IV access, and increased strain on time and resources of medical centers and healthcare professionals. A fixed-dose combination of pertuzumab and trastuzumab for subcutaneous (SC) injection (pertuzumab, trastuzumab, and hyaluronidase-zzxf (PHESGO®, F. Hoffmann-La Roche Ltd, Basel, Switzerland; PH FDC SC)) has been approved for use alongside chemotherapy for early-stage and metastatic HER2-positive BC.

Objectives This systematic literature review was performed to identify evidence relating to time/resource use and resulting cost differences between SC and IV administration of oncology biologics in a hospital setting, and, ultimately, to inform economic modeling and associated health technology assessment of PH FDC SC.

Methods Electronic databases (Embase, MEDLINE, and EconLit) were searched on 9 April 2020. Additional hand searches were performed to identify publications not captured in the electronic database search. Publication screening and data extraction (study characteristics, participants, interventions, costs, and time/resource use) were carried out per the standard Cochrane review methodology. The quality of economic evidence of cost analyses was assessed using the 36-item checklist of the National Institute for Health and Care Excellence Single Technology Appraisal Specification for submission of evidence (January 2015).

Results The database search identified 2,740 records, of which 237 underwent full text screening. Full text screening, prioritization of publications about patients with a cancer diagnosis, and the addition of four citations identified during the hand search resulted in 72 final included publications, relating to 71 unique studies. This included 40 publications that described the time/resource use and/or costs associated with SC versus IV trastuzumab administration for the treatment of HER2-positive BC, and 28 publications that described time/resource use and/or costs associated with rituximab SC versus IV administration for the treatment of non-Hodgkin’s lymphoma/follicular lymphoma and diffuse large B-cell lymphoma. The majority of publications showed substantial time savings for preparation and administration of SC versus IV therapy, and cost savings associated with reductions in healthcare professional time and resource use for SC administration.

Limitations There was a lack of consensus between publications regarding time and cost measurements. In addition, the search was limited to publications related to anticancer drugs; the majority of the studies included were performed in European countries.

Conclusions and implications This review indicated a substantial body of evidence showing time/resource and cost savings of SC versus IV administration of oncology biologics in a hospital setting, which can be used to inform economic evaluations of PH FDC SC.

Extended author information available on the last page of the article
1 Introduction

Breast cancer (BC) is the most prevalent form of invasive cancer among women, with over 2.2 million cases and almost 700,000 deaths worldwide in 2020 [1, 2]. Approximately 20% of BC cases are human epidermal growth factor receptor 2 (HER2)-positive, a subtype defined by amplification of the HER2 oncogene and overexpression of the HER2 transmembrane receptor protein on the surface of tumor cells. HER2 interacts with other HER family proteins as part of signal transduction pathways, mediating cell growth, survival, and differentiation [3]. HER2-positive BC is associated with poor prognosis, arising from increased tumor aggressiveness, higher rates of recurrence, and increased mortality [3, 4].

Trastuzumab (Herceptin®, F. Hoffmann-La Roche Ltd, Basel, Switzerland), the first approved HER2-targeted monoclonal antibody, transformed the treatment and prognosis of patients with HER2-positive BC in both the early and the metastatic settings [5–15]. This has led to the development of dual anti-HER2 blockade with pertuzumab plus trastuzumab (PERJETA® and Herceptin®, F. Hoffmann-La Roche Ltd; standard of care in first-line HER2-positive metastatic BC (MBC) and high-risk early BC (EBC)) [13–21] and the anti-HER2 antibody-drug conjugate ado-trastuzumab emtansine (Kadcyla®, F. Hoffmann-La Roche Ltd; used in second-line HER2-positive MBC and in EBC for the treatment of residual invasive disease following neoadjuvant therapy and surgery) [13–16, 22–24]. These treatment options have improved the prognosis for patients with HER2-positive BC substantially.

However, intravenous (IV) administration of anticancer biologics can present multiple challenges for many patients, including long infusion and observation times, the need for repeated, invasive IV access (sometimes over long periods of time in cases where there is evidence of a treatment response), and the potential risks associated with indwelling venous access (e.g., catheter-associated pain/discomfort, thrombosis, or risk of systemic infections) [25–28]. Moreover, the increasing use of IV administered agents in oncology has placed a strain on medical centers and healthcare professionals (HCPs) with respect to the time and resources required to prepare and administer infusions [25, 29].

A subcutaneous (SC) formulation has previously been developed for trastuzumab (Herceptin® SC or Herceptin Hyllecta™, F. Hoffmann-La Roche Ltd) [11, 30]. The HanNaH study (NCT00950300) compared the pharmacokinetics, efficacy, and safety of SC trastuzumab with IV trastuzumab. SC trastuzumab was shown to be non-inferior to IV, for both co-primary endpoints (serum trough concentration at pre-dose cycle 8 and pathologic complete response rates), demonstrating that the SC formulation is a valid treatment alternative to IV [31–34]. Further to this, the safety and efficacy profiles for SC trastuzumab in combination with IV pertuzumab and docetaxel as a first-line treatment for patients with HER2-positive MBC in the MetaPHER study (NCT02402712) was found to be consistent with those observed for IV trastuzumab in combination with IV pertuzumab and docetaxel in the CLEOPATRA study (NCT00567190) [21, 35–38].

The PrefHer study (NCT01401166), in which patients with EBC were randomized to receive four cycles of SC trastuzumab followed by four cycles of IV trastuzumab, or vice versa, demonstrated a strong patient preference and increased HCP satisfaction with SC over IV administration [39, 40]. These results were also confirmed in the metastatic setting in the MetaspHer study (NCT01810393) [41]. The approval of a fixed-dose combination of pertuzumab and trastuzumab for SC injection (pertuzumab, trastuzumab, and hyaluronidase-zzxf (PHESGO®, F. Hoffmann-La Roche Ltd; PH FDC SC)) [42] presents an opportunity for an option that is preferred by patients and can potentially provide time-saving benefits to patients and HCPs versus IV administration, according to patient and HCP questionnaires in the PHranceSCa study (NCT03674112) [43].

This systematic literature review (SLR) was performed to identify evidence relating to differences in time/resource use and the resulting cost differences between SC and IV administration (but not differences in the drug costs themselves). The rationale for performing the SLR was as preliminary work that will ultimately inform economic modeling and associated health technology assessment of PH FDC SC. The most analogous evidence was likely to be data relating to the time/resource use and cost differences for SC versus IV administration of trastuzumab for the treatment of BC, or of rituximab (Rituxan® or MabThera®, F. Hoffmann-La Roche Ltd) for treatment of non-Hodgkin’s lymphoma (NHL)/follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). Thus, the SLR initially sought to
identify cost analyses as well as time-and-motion analyses for any indication where patients’ treatment requires IV or SC administration in a hospital setting, and was then restricted to oncology biologics.

2 Methods

A systematic search was conducted via the Ovid platform (Wolters Kluwer, Alphen aan den Rijn, Netherlands) on 9 April 2020 using a predefined search strategy within the Embase (1980–present), MEDLINE (1946–present), and EconLit (1961–present) electronic databases. The database search strings identified all relevant studies (full papers or abstracts from any conferences) indexed in Embase, and were modified for performing searches in MEDLINE and EconLit to account for differences in syntax and thesaurus headings. Searches included terms for free text and Medical Subject Heading (MeSH) terms. The search strategies used and details of any additional hand searches that were carried out to identify publications not captured in the electronic database search are provided in the Online Supplemental Material, Resource 1. Details on the study eligibility criteria are presented in Table 1.

The SLR followed the standard Cochrane review methodology [44] and included double screenings by two independent reviewers. Relevant data from included publications were extracted by a reviewer and verified by a second independent reviewer; any disputes were resolved through discussion. The types of data to be collected were predefined and included: study country, study design, industry sponsor, inclusion/exclusion criteria, target population, study aims, data source, intervention, study limitations, and conclusions. Cost and time/resource use outcomes were also captured and stratified by disease and route of administration. Quality assessments of the studies in the included publications were conducted by a single analyst and verified by a second analyst or project lead. The quality of economic evidence reported in the included cost analysis publications were assessed using the 36-item checklist of the National Institute for Health and Care Excellence Single Technology Appraisal Specification for manufacturer/sponsor submission of evidence (January 2015), adapted from Drummond and Jefferson [45]. The methodologic limitations of publications reporting on time/resource use and costs were assessed based on a model described by Drummond et al. [46] and adapted to cost of illness by Molinier et al. [47].

3 Results

This search identified 2,740 records, of which 237 underwent full-text screening. Ninety-five publications were excluded during full-text screening, leaving 142 potentially eligible publications, a higher number than anticipated due to broad eligibility criteria. Prioritization was therefore given to publications of patients with a cancer diagnosis, as noted in Table 1, given the target population for PH FDC SC, resulting in exclusion of 74 non-oncology publications. Hand searching identified a further four citations that met the revised eligibility criteria, resulting in 72 final included publications, relating to 71 unique studies. The PRISMA diagram is presented in Fig. 1.

3.1 Characteristics of Included Studies

Table 2 summarizes the characteristics of all included studies. In total, 40 publications were identified that described the time/resource use and/or costs associated with SC versus IV trastuzumab administration for the treatment of HER2-positive BC. Of these, 22 publications [25, 48–68] (13 full papers [25, 51–55, 59, 62–67] and nine abstracts [48–50, 56–58, 61, 68]) reported time/resource use for administration of SC versus IV trastuzumab (Fig. 2). This included two publications related to PrefHer, a multinational study conducted in eight countries (Canada, France, Switzerland, Denmark, Italy, Russia, Spain, and Turkey), 18 publications that reported studies that were conducted in at least 12 individual European countries (the country was not stated in one of the publications) [48–54, 57–61, 63–68], one publication that reported a study in Hong Kong [56], and one that reported a study in New Zealand [62]. A total of 24 publications reported on the costs of SC versus IV trastuzumab administration. Of these, 19 reported data for at least 13 individual European countries (the country was not stated in one of the publications) [48–51, 53, 54, 57, 59–61, 63–65, 67]. The other five were in Canada, Chile, Singapore, Hong Kong, and New Zealand [56, 62, 69–71]. Budget impacts of introducing SC trastuzumab were reported by five publications (Arabia, Ecuador, Canada, Brazil, Spain) [69, 72–75]. Six other publications described costs related to SC trastuzumab: three compared SC trastuzumab with an IV trastuzumab biosimilar [76–78], two described cost minimization analyses for SC versus IV administration [79, 80], and one reported on cost savings for the administration of the SC route over 18 months compared with a combination of SC and IV [81].

A total of 28 publications were identified that described time/resource use and/or costs associated with rituximab SC versus IV administration for the treatment of NHL/FL or DLBCL. Nineteen of these publications reported on time/resource use, 11 of which also described related costs. There were an additional seven publications that reported only on costs, to give 18 publications with cost-related analyses. The remaining three publications described the likely budget impact of introducing the rituximab SC formulation for the treatment of NHL or DLBCL, and provided limited
evidence relating to the comparative costs of rituximab SC and administrations.

### 3.2 Quality Assessment Results

A quality assessment of all full publications was conducted. Overall, the studies were considered to be of adequate quality. However, due to the wide range of study designs and the paucity of studies reporting individual outcomes, it was not feasible to categorize the studies according to risk. Although the study designs of the economic evaluations were generally well described, reporting of data collection methods and of analysis and interpretation of the results was inconsistent between studies. For example, time horizons of costs and benefits, discount rates, and sensitivity analyses were only discussed in a small proportion of the publications.
3.3 Time/Resource Use With IV Versus SC Administration of Trastuzumab

Of the 22 publications reporting data regarding time required, or the difference in time required, for administration of SC versus IV trastuzumab for the treatment of BC, 16 reported data either from time-and-motion studies or studies where the time for each specific procedure was directly measured. Some reported single-center studies, while others reported studies involving up to 16 centers. Two publications reported studies that estimated time based on information provided by drug preparation/administration software [51, 68]; one publication reported a study that estimated time from a survey of HCPs [66], and three publications did not report the manner in which time was estimated [52, 56, 58].

HCP time includes drug preparation and administration times, and may be reported according to specific roles (e.g., pharmacists, nurses, nursing assistants), or as an average of the HCP times. Variation in the description of the elements involved in preparation and administration of trastuzumab may limit comparison between publications. For example, one time-and-motion study publication [63] described the measured time for each step involved in preparation and administration, including involvement of the pharmacist, staff nurse, and clinical nurse specialist, and then provided the average HCP time required for administration based on this. Another publication [53] only reported active HCP times for preparation and administration, obtained from detailed case reports and stopwatch time measurements for all nurse activities for a subgroup of observed cases.

3.3.1 Preparation Time

Preparation time for trastuzumab was reported in seven publications, including two where only the difference in preparation time between SC and IV was reported. Within these, preparation time was directly measured [25, 49, 53, 62] or estimated from software records [51, 68] or HCP questionnaires [66]. HCP estimates were consistent with publications from studies in which time was measured directly. Preparation of IV trastuzumab for administration was reported to require 14–21 min, compared with 0–11 min for SC trastuzumab. The time difference between SC and IV was 3–14 min per preparation [25, 49, 51, 53, 62, 66, 68]. An additional publication reported preparation time for the loading dose to be 8 versus 2 min, for IV and SC trastuzumab, respectively. Nursing time was reported as 16 versus 7 min, and was deemed likely to relate to preparation rather than administration of the dose, giving a total time of 24 versus 9 min [61].
| Publication | Study country | Study design and aim | Data source | Patient population and intervention | Cost outcomes identified | Time/resource-use outcomes identified |
|-------------|---------------|----------------------|-------------|---------------------------------------|--------------------------|---------------------------------------|
| Trastuzumab—full publications | | | | | | |
| De Cock 2016 [25] | Canada, France, Switzerland, Denmark, Italy, Russia, Spain, Turkey | Prospective, observational time-and-motion study (PrefHer; NCT01401166) to quantify patient chair time and active HCP time associated with SC and IV trastuzumab<sup>a</sup> | Multiple centers across different countries | HER2-positive BC (NR) 1) SC trastuzumab (single-use injection device or handheld syringe) 2) IV trastuzumab | – | Treatment room time, 17.9 versus 9.8–11.2 min, Preparation, 13.9 versus 5.0–7.6 min Total time, 31.8 versus 14.8–18.8 min, i.e. 13–17 min shorter Chair time, 55–57 min shorter; 77.8 versus 20.9–22.6 min, p<0.0001 |
| Farolfi 2017 [51] | Italy | Retrospective cohort study to compare the time/resource utilization of SC and IV trastuzumab and to conduct an economic evaluation<sup>a</sup> | Time/resource utilization retrieved from Institutional medical record database (Log80); unit costs for healthcare professionals retrieved from the Italian National Contract | EBC (n = 114) 1) SC trastuzumab 2) IV trastuzumab | Direct costs, €13,655 versus €14,154/patient/year €14,233 versus €14,273/patient/year (including indirect costs) Preparation, €92.60 versus €57.50/patient/year Day hospital cost, €575.82 versus €61.51/patient/year | Preparation, 14.1 versus 10.7 min Administration, 90 versus 5 min (loading dose); 30 versus 5 min (maintenance dose) |
| Hedayati 2019 [54] | Sweden | Retrospective study to estimate the economic efficiency of SC trastuzumab by assessing the economic benefits of actual SC-driven process changes at one single Swedish healthcare institution<sup>a</sup> | Karolinska University Hospital | HER2-positive BC (n = 178) 1) IV trastuzumab 2) SC trastuzumab | Savings for cohort over 1 year: Avoiding surgery to implant catheters, €419,012 Preparation time, €167,087 Consumables, €17,389 Direct cost saving, €603,488 (for cohort over 1 year) | Administration, 90 versus 10 min (first session); 30 versus 10 min (subsequent sessions) |
| Jackisch 2015 [55] | Canada, Denmark, France, Russia, Spain, Switzerland | Prospective study to provide an overview of the study data on SC trastuzumab and summarizes and evaluates the experience of 7 German centers over 18 months of administering SC trastuzumab in routine clinical practice<sup>a</sup> | NR | HER2-positive BC (n = 415) 1) IV trastuzumab 2) SC trastuzumab | – | Active HCP time: Denmark, 7.2 versus 4.9 min France, 9 versus 5.7 Canada, 11.8 versus 6.3 Russia, 9.9 versus 5.2 Spain, 8.2 versus 4.0 Switzerland, 10.5 versus 7.2 Chair time: Denmark, 57 versus 24 min France, 85 versus 27 Canada, 67 versus 24 Russia, 47 versus 13 Spain, 100 versus 20 Switzerland, 133 versus 38 |
| Publication          | Study country | Study design and aim                                                                 | Data source | Patient population and intervention | Cost outcomes identified                                                                 | Time/resource-use outcomes identified |
|---------------------|---------------|-------------------------------------------------------------------------------------|-------------|-------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------|
| Lopez-Vivanco 2017  | Spain         | Prospective observational study to describe HCP and patient time and related costs associated with IV and SC trastuzumab in patients with HER2-positive early BC<sup>a</sup> | NR          | HER2-positive BC (n = 10)           | Preparation and administration, €12.76 versus €6.01                                      | Active HCP time, 27.2 versus 13.2 min |
|                     |               |                                                                                     |             | 1) IV trastuzumab                   | Consumables, €8.64 versus €2.39                                                          | [Nursing time, 21.8 versus 11.2 min  |
|                     |               |                                                                                     |             | 2) SC trastuzumab                   | Costs per 18 cycles: HPC, €230 versus €108                                              | Pharmacist time, 4.2 versus 1.2 min    |
|                     |               |                                                                                     |             |                                    | Consumables, €155 versus €43                                                             | Nursing assistant time, 1.1 versus 0.8 min |
|                     |               |                                                                                     |             |                                    | Drug costs, €29,046 versus €28,301                                                       | Chair time, 101 versus 20 min         |
|                     |               |                                                                                     |             |                                    | Direct costs, €29,432 versus €28,52 (for 18 cycles)                                      | Treatment room time, 120 versus 30 min |
|                     |               |                                                                                     |             |                                    | Nursing assistant time, 1.1 versus 0.8 min                                              | Hospital time, 205 versus 115 min     |
|                     |               |                                                                                     |             |                                    | Lost productivity, €204 versus 51 (for 18 cycles)                                        |                                       |
|                     |               |                                                                                     |             |                                    | Pharmacy costs, €29,046 versus €28,301                                                    |                                       |
|                     |               |                                                                                     |             |                                    | Preparations and administration, €230 versus €108                                        |                                       |
|                     |               |                                                                                     |             |                                    | Total time, 184 min                                                                      |                                       |
| North 2015 [62]     | New Zealand  | Noninterventional, descriptive study to determine medical time/resource utilization associated with administration of SC trastuzumab injection via handheld syringe versus IV trastuzumab infusion in patients with HER2-positive BC in New Zealand<sup>a</sup> | Auckland City Hospital (IV trastuzumab) and Tauranga Hospital (SC and IV trastuzumab) | HER2-positive BC (n = 18) | Total, NZD 76.94 For administration and preparation, NZD 61.67 [Chair time, NZD 40.03] HCP nurse time, NZD 4.59 Total pharmacist time, NZD 17.05 Consumables, NZD 15.27 | Pharmacist time, 20.5 versus 0 min Administration, 37.6 versus 5.7 min HCP (nurse) time, 13.0 versus 6.9 min Chair time, 47.4 versus 10.5 min |
| O’Brien 2019 [63]   | Ireland       | Prospective observational study to analyze which route of trastuzumab administration, for the treatment of HER2-positive BC, was more cost-effective and time-saving in relation to active HCP time<sup>a</sup> | Two large acute Irish University teaching hospitals within the south/southwest | HER2-positive BC (NR) 1) IV trastuzumab 2) SC trastuzumab | Consumables, €56.28 versus €25.91 Preparations and administration, €44.93 versus €9 Direct costs, for 17-cycle treatment €36,619 versus €35,010 €36,863 versus €35,077 (including indirect costs) Societal costs, for 17-cycle treatment €243.74 versus €67.15 | HCP time, 74.7 versus 15.4 min |
| Publication     | Study country | Study design and aim                                                                 | Data source         | Patient population and intervention | Cost outcomes identified                                                                 | Time/resource-use outcomes identified |
|-----------------|---------------|--------------------------------------------------------------------------------------|---------------------|-------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------|
| Olofsson 2016 [64] | Sweden        | Observational study to estimate the societal value of trastuzumab administered through SC injection compared to IV infusion\(^b\) | Five oncology clinics | HER2-positive BC \(n = 195\) 1) IV trastuzumab 2) SC trastuzumab | Direct costs, First visit, \(€2695\) versus \(€1938\) 2033 versus \(€1933\) 2099 versus \(€1983\) (including indirect costs) First visit: Nurse time, \(€15\) versus \(€8\) Drug costs, \(€2616\) versus \(€1920\) Subsequent visits: Nurse time, \(€15\) versus \(€8\) Drug costs, \(€1962\) versus \(€1920\) First visit: Lost productivity, \(€94\) versus \(€16\) Lost leisure time, \(€187\) versus \(€125\) (includes patient and accompanying kin) Subsequent visits Lost productivity, \(€26\) versus \(€16\) Lost leisure time, \(€40\) versus \(€34\) | HCP time, 44 versus 26 min (first treatment) 30 versus 16 (subsequent treatment), \(p < 0.01\) for both Hospital time: 414 versus 313 min (first treatment), \(p < 0.05\); 90 versus 67 min, \(p < 0.01\) (subsequent treatment) |
| Olsen 2018 [65] | Denmark       | Study design NR. To estimate the costs of administration of IV and SC trastuzumab treatment\(^a\) | Seven departments located at regional hospitals and five at university hospitals | HER2-positive BC (NR) 1) IV trastuzumab 2) SC trastuzumab | Non-drug costs excluding patient’s time: 1st cycle, \(€171\) versus \(€60\) 4+ cycle, \(€103\) versus \(€52\) Non-drug costs including patient’s time: 1st cycle, \(€290\) versus \(€153\) 4+ cycle, \(€112\) versus \(€55\) | HCP time, 92 versus 30 min (first cycle), subsequent therapy, 56 versus 30 min Direct contact, 111 versus 13 min (first cycle), 51 versus 13 min (subsequent cycle) Observation time, same for first cycle; second cycle, 61 versus 93 min |
| Tjalma 2018 [67] | Belgium       | Observational, non-interventional, prospective, monocentric time, motion and cost assessment study to determine and compare the time and costs of SC versus IV trastuzumab administration in patients with HER2-positive BC\(^a\) | LEAN day care oncology unit of the Antwerp University Hospital | HER2-positive BC \(n = 130\) 1) SC trastuzumab 2) IV trastuzumab | Administration, \(€224.48\) versus \(€10.60\) HCP time, \(€3.74\) versus \(€7.9\) Consumers, \(€23.60\) versus \(€2.70\) Drug wastage, \(€139.00\) versus 0 Overall saving per administration excluding drug costs, \(€212.93\) | Total time in center, 173 versus 51 min HCP time, 68 versus 14 min Chair time, 137 versus 10.6 min |
| Publication                          | Study country | Study design and aim                                                                                                                                                                                                 | Data source                                                                 | Patient population and intervention                                                                 | Cost outcomes identified                                                                 | Time/resource-use outcomes identified |
|-------------------------------------|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------|
| Rojas 2020 [71]                     | Chile         | Cost-minimization analysis to compare the direct and indirect medical and non-medical costs associated with SC trastuzumab and IV trastuzumab in patients with HER2+ early BC in a private health center in Chileb | Nuestra Señora de la Esperanza Cancer Center, Red de Salud UC-Christus network | HER2-positive BC (n = 100) 1) IV trastuzumab 2) SC trastuzumab                                                        | Direct costs, per treatment (18 doses) including indirect costs, US$83,309 versus US$77,068 Per treatment (18 doses): Preparation, US$78,076 versus US$73,225 Administration, US$3485 versus US$2005 Aes, US$1574 versus US$1715 Societal costs, per treatment (18 doses) Indirect costs, US$173 versus US$1216 | –                                     |
| De La Vega Zamorano 2017 [81]       | Spain         | Retrospective observational study to evaluate and quantify the economic impact of SC presentation of trastuzumab                                                                                                                                                     | Hospital de la Ribera. Alzira. Valencia                                                                                   | HER2-positive EBC or MBC (n = 28) 1) SC trastuzumab 2) IV trastuzumab                                                                 | Direct costs, annual saving, €35,332                                                      | –                                     |
| Lazaro Cebas 2017 [82]              | Spain         | Cross-sectional questionnaire-based study to investigate patient satisfaction and preferences regarding SC versus IV trastuzumab and to evaluate the financial impact derived from the use of the SC formulationa | Oncology outpatient hospital (Hospital Universitario 12 de Octubre, Madrid)                                                | HER2-positive BC (n = 76) 1) IV trastuzumab 2) SC trastuzumab                                                                 | –                                                                                         | –                                     |
| Mylonas 2017 [86]                   | Greece        | Economic analysis to conduct an economic evaluation comparing SC trastuzumab with IV trastuzumab, in the treatment of patients with HER2-positive early and metastatic BC (EBC-MBC), in the Greek health care settinga | NR                                                                                                                     | HER2-positive BC (NR) 1) IV trastuzumab 2) SC trastuzumab                                                                 | Direct costs, €23,118 versus €21,870 per therapy Administration, €266.94 versus €64.41 CVAD, €289.80 versus 0 Overhead, €249.94 versus €67.19 Drug cost, €22,311 versus €21,738 | –                                     |
| Publication     | Study country | Study design and aim                                                                                                                                                                                                 | Data source                                                                                   | Patient population and intervention                                                                 | Cost outcomes identified                  | Time/resource-use outcomes identified |
|----------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------|---------------------------------------|
| Trastuzumab—abstracts                                                                                                                             |                                                                                               |                                                                                               |                                                                                                       |                                          |                                        |
| Andrade 2013 [48] | Portugal     | Study design NR. To determine the costs associated with the preparation and administration of HER2-positive BC treatment with IV trastuzumab and to estimate the difference compared with SC trastuzumab                                       | Five public and two private hospitals; official sources or price tables provided by manufacturer | HER2-positive BC (mean: n = 12 patients/week) 1) IV trastuzumab 2) SC trastuzumab                     | €43.22 versus €3.18                      | –                                     |
| Blein 2018 [49]  | France       | Observational study to evaluate the organizational and economic impacts generated by the administration of SC versus IV trastuzumab                                                                                         | Nine healthcare facilities                                                                                                                             | HER2-positive BC (n = 411) 1) SC trastuzumab 2) IV trastuzumab                                      | Consumables, €11.07 lower               | Preparation, 12 min shorter Administration, 107 min shorter |
| De Cock 2014 [50] | Russia       | Prospective, time-and-motion study to quantify HCP time and patient chair time related to trastuzumab treatment to estimate potential time and cost savings with a transition from IV to SC                                            | Three centers                                                                                                                              | HER2-positive BC (NR) 1) IV trastuzumab 2) SC trastuzumab                                       | HCP time, 1175 roubles saved for 18 sessions Chair time, 6314 roubles saved for 18 sessions | HCP time, 38.7 versus 20.1 min, 18.6 min shorter Chair time, 67.1 versus 7.6 min, 59.5 min shorter |
| Lee 2018 [56]    | Hong Kong    | Cost-minimization analysis to investigate the cost differences between IV and SC trastuzumab in Hong Kong by applying the medical time/resources utilization data in other countries                                          | NR                                                                                                                                            | HER2-positive BC (NR) 1) IV trastuzumab 2) SC trastuzumab                                       | Saving for 18-cycle treatment: HCP time costs, HKD 4416 Drug costs: HKD 73,720 | Nursing time, 0.18 FTE per week saved Pharmacist time, 0.14 FTE saved per week |
| Lewis 2017 [57]  | UK           | Retrospective study to evaluate the impact of SC trastuzumab on out-patient BC services at the Royal United Hospital, Bath and to determine the necessity for prolonged observation after its administration                          | Royal United Hospital, Bath BC (NR) 1) SC trastuzumab 2) IV trastuzumab                                                                                | Saving for given year: Consumables, £2220 Drug costs £94,327                                     | HCP time, 15 min saved Chair time, 38 min saved |                                        |
| Lopez 2017 [58]  | NR           | Retrospective study to evaluate the impact on drug costs, patient chair time and safety profile of switching from IV to SC trastuzumab                                                                             | NR                                                                                                                                            | HER2-positive BC (n = 74) 1) IV trastuzumab 2) SC trastuzumab                                     | –                                        | Chair time, 6-fold reduction over 1 year |

**Notes:**
- NR: Not reported.
Table 2 (continued)

| Publication         | Study country       | Study design and aim                                                                 | Data source                                                   | Patient population and intervention | Cost outcomes identified                                                                 | Time/resource-use outcomes identified |
|---------------------|---------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------|
| Nestorovska 2015 [60] | Republic of Macedonia | Cost-minimization analysis to compare the total cost of SC trastuzumab versus IV trastuzumab for HER2-positive BC patients from the Republic of Macedonia<sup>a</sup> | Data from prior prospective time-motion study; unit costs obtained utilizing official (government and hospital pharmacy) publicly available data | EBC (<i>n</i> = 169) 1) SC trastuzumab 2) IV trastuzumab | Direct costs, €30,500 versus €30,102 per treatment course Non-drug costs, €196 versus €420 | Preparation and administration, 47 min saved |
| Nierenberger 2017 [61] | France | Time-motion study to compare times (preparation, nurse and medical) and costs of IV trastuzumab and SC trastuzumab<sup>a</sup> | Hospital | HER2 positive BC (NR) 1) SC trastuzumab 2) IV trastuzumab | Consumables, 655 versus €240 Nurse time, 15.7 versus 7.0 min | Preparation, 8.3 versus 2 min (first dose); 6.5 versus 2 min (subsequent doses) |
| Coombes 2019 [69] | Canada | Cost-minimization analysis to estimate the incremental costs/savings associated with the use of SC trastuzumab for the treatment of HER2-positive BC if reimbursed with the same provincial funding criteria as IV trastuzumab in Ontario, Canada<sup>a</sup> | NR | HER2-positive BC (NR) 1) IV trastuzumab 2) SC trastuzumab | Savings of Can$11,943 per treatment course BIM savings Year 1, Can$15.8 million Year 2, Can$19.4 million Year 3, Can$23.0 million | – |
| Ali 2017 [72] | Kingdom of Saudi Arabia | Budget impact model to estimate financial impact of introducing fixed dose SC trastuzumab for treatment of HER2-positive EBC in KSA<sup>a</sup> | Clinical and cost inputs were obtained through discussion with medical oncologists and hematologists; outputs from budget impact model | HER2-positive EBC (NR) 1) SC trastuzumab 2) IV trastuzumab | BIM, total savings over 3 years: 7.2–9.4% and 12.4–16.6% (assuming 25% and 50% reductions in non-drug costs) | – |
| Kashiura 2018 [73] | Brazil | Economic analysis to estimate the budgetary impact of SC trastuzumab, compared with IV trastuzumab, in the Brazilian Private Healthcare System, to treat early and metastatic HER-2 positive BC<sup>a</sup> | Data from National Regulatory Agency for Private Health Insurance and Plans; data from Survey performed with 28 HMOs | HER2 positive BC (<i>n</i> = 31,909) 1) SC trastuzumab 2) IV trastuzumab | BIM savings over 5 years, 948.2 million BRL | – |
| Poquet-Jornet 2018 [74] | Spain | Economic analysis to assess the hospital budget impact of only SC trastuzumab against IV + SC trastuzumab for patients with BC<sup>a</sup> | RWD from Hospital Marina Salud de Denia and electronic records | HER2-positive BC (<i>n</i> = 58) 1) IV trastuzumab 2) SC trastuzumab | BIM, current scenario (66% receiving iv), €466,480 All patients receiving IV, €393,654 | – |
| Publication | Study country | Study design and aim | Data source | Patient population and intervention | Cost outcomes identified | Time/resource-use outcomes identified |
|-------------|---------------|----------------------|-------------|-------------------------------------|--------------------------|------------------------------------|
| Calvache 2017 [75] | Ecuador | Economic analysis to conduct an economic analysis for decision making between IV and SC trastuzumab for the treatment of HER2-positive BC in Ecuador | NR | HER2-positive BC (n = 515) 1) IV Trastuzumab 2) SC Trastuzumab | BIM, IV, year 1, US$15,711,000 IV, year 2, US$15,199,000 SC, year 1/2, US$14,842,000 Saving over 5 years, US$2,296,000 | – |
| Agirrezabal 2018 [76] | Italy | Cost-saving study to analyze the per-patient costs and potential savings of KANJINTI® compared with originator Herceptin® and other trastuzumab biosimilars (IV) in HER2-positive EBC and MBC and MGC in Italy | Official, public drug prices | HER2-positive BC and gastric cancer (NR) 1) KANJINTI® IV 2) Herceptin® IV 3) Herceptin® SC | – | Preparation and administration, 79 versus 18 min |
| D’Arpino 2019 [77] | Italy | Study design NR. To compare the total medical costs for a hospital of treatment with subcutaneously injected Herceptin® and intravenously infused KANJINTI® | A single hospital institution | HER2-positive EBC or MBC and metastatic gastric cancer (NR) 1) Herceptin® SC 2) KANJINTI® IV | – | |
| Todorovic 2017 [79] | Montenegro | Economic analysis to compare the total cost of SC trastuzumab versus IV trastuzumab (IV-TRA) for HER2-positive patients with BC at the Oncology Department at Clinical Center of Montenegro | Oncology Department at Clinical Center of Montenegro | HER2-positive BC (n = 55) 1) IV trastuzumab 2) SC trastuzumab | – | |
| Villarreal-Garza 2019 [80] | Mexico | Economic analysis to estimate the cost savings of the use of SC trastuzumab compared with IV trastuzumab according to patient weight, and calculate the infusion time of SC trastuzumab in a tertiary healthcare facility at TecSalud from Feb 2018–Jan 2019 | Tertiary healthcare facility at TecSalud | HER2-positive BC (NR) 1) SC trastuzumab 2) IV trastuzumab | – | |
| Publication       | Study country | Study design and aim                                                                 | Data source       | Patient population and intervention                                      | Cost outcomes identified                                                                 | Time/resource-use outcomes identified |
|------------------|---------------|-------------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------|
| Kulikov 2015 [83] | Russia        | Economic analysis to determine the preferable treatment scheme for BC from the pharmaco-economic perspective by the comparison of SC and IV administrationa | NR                | BC (NR)  
1) IV trastuzumab  
2) SC trastuzumab | Direct costs, €25,016 versus €21,863  
Saving of €3153 per treatment course | –                      |
| Martin 2017 [84]  | Panama        | Cost minimization study to carry out a cost minimization study considering the cost of the treatment, the supplies and the time utilized by Pharmacy and Nursing to prepare and administer it (IV, SC trastuzumab)a | Instituto Oncológico Nacional | NR (NR)  
1) IV trastuzumab  
2) SC trastuzumab | Drug costs, 17% saving  
Nursing supplies, 87% saving  
Pharmacy supplies, 47% saving  
Nursing time costs, 91% saving  
Pharmacy time costs, 69% saving  
Direct costs, US$5985/patient/year (18-cycles) | –                      |
| Mitchell 2019 [85] | UK            | Economic analysis to compare and determine the experience of patients receiving all of their trastuzumab treatment via the IV route versus the SC routea | The Christie NHS Foundation Trust | HER2-positive BC (n = 116)  
1) SC trastuzumab  
2) IV trastuzumab | –                                                                 | –                      |
| Favier 2018 [52]  | France        | Observational study to evaluate the medical and economic consequences of switching to SC trastuzumab and SC rituximaba | 36 day hospitals | Patients with cancer (NR)  
1) IV trastuzumab/rituximab  
2) SC trastuzumab/rituximab | –                                                                 | Chair time trastuzumab, reduced by 56%  
Chair time rituximab, reduced by 74%                                                                 |
| Publication          | Study country | Study design and aim                                                                 | Data source                                                                                          | Patient population and intervention                                                                 | Cost outcomes identified                                                                 | Time/resource-use outcomes identified |
|---------------------|---------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------|
| Franken 2018 [53]   | The Netherlands | Observational noninterventional micro costing study to investigate time/resource use for hospitals and patients and compared healthcare and societal costs for IV and SC administration of trastuzumab and rituximab<sup>b</sup> | NR                                                                                                   | HER2-positive EBC or MBC or NHL (n = 126)                                                                  | Trastuzumab Direct costs, €1856 versus €1763 Total direct costs excluding drug costs, €118 versus €50 | Preparation, 17.1 versus 8.4 min Administration, 97.4 versus 6.6 min Active HCP time, 44.5 versus 29.7 min |
| Cicchetti 2018 [105]| Italy         | Economic analysis to provide a multidimensional assessment of the impact of SC rituximab and trastuzumab compared with IV, providing a particular focus on expected social and economic benefits for the patient<sup>f</sup> | NR                                                                                                   | Patients with cancer (NR) 1) IV trastuzumab/rituximab 2) SC trastuzumab/rituximab                         | Direct costs, €4050 saving per patient per year                                            | –                                    |
| Vanghelauwe 2018 [68]| France        | Cost analysis study to evaluate the realized and potential medico-economic benefits in OCUs induced by the use of SC rituximab and SC trastuzumab<sup>a</sup> | Data obtained from chemotherapy prescription software, Medical Information System 2016, patient satisfaction surveys and interviews with hematologists, oncologists, nurses and pharmacists | Patients with cancer (NR) 1) IV trastuzumab/rituximab 2) SC trastuzumab/rituximab                           | –                                                                                        | Preparation, 8.9 min saved HCP, 6.8 min saved Chair time, 3 versus 2 hours |
| Publication | Study country | Study design and aim | Data source | Patient population and intervention | Cost outcomes identified | Time/resource-use outcomes identified |
|-------------|---------------|----------------------|-------------|-------------------------------------|--------------------------|--------------------------------------|
| Ghosh 2018 [70] | Singapore | Cost-minimization analysis to analyze cost-differences between SC versus IV trastuzumab for EBC and MBC in Singapore<sup>a</sup> | NR | EBC or MBC (NR) | Non-drug savings, US$22,449 versus US$4036, 17% of total savings for 26 cycles | – |
| Jang 2018 [78] | UK | Economic analysis to assess the budget impact of adopting IV biosimilar rituximab and IV biosimilar trastuzumab compared with SC and IV originators from the perspective of the UK National Health Service<sup>c</sup> | Drug acquisition and administration costs obtained from national tariffs | Rheumatoid arthritis, chronic lymphocytic leukemia, NHL, granulomatosis with polyangiitis and microscopic polyangiitis, BC and MGC (NR) | 1) SC trastuzumab/rituximab  2) IV trastuzumab/rituximab | – |
| Ponzetti 2016 [66] | Italy | Systematic survey to analyze the time/resource and cost implications from different perspectives (patient, medical staff) in the real world| Nineteen centers across six regions: Emilia Romagna, Lazio, Liguria, Piemont, Toscana, Umbria | NHL and BC (NR) | 1) Rituximab SC  2) Rituximab IV | – |
| De Cock 2016b [88] | Austria, Brazil, France, Italy, Russia, Slovenia, Spain, UK | Prospective time-and-motion study (MabCute; NCT01461928) to quantify active HCP time as well as chair time associated with rituximab IV and SC administrations in patients with iNHL, and to estimate the potential time savings with a conversion from rituximab IV to SC, for a single administration session and for the first year of treatment| Eight countries and 30 day oncology units | iNHL (NR) | 1) Rituximab SC  2) Rituximab IV | – |
| Lugtenburg 2017 [89] | The Netherlands, Turkey, Spain, Switzerland, Germany | Randomized, open-label study to examine the efficacy and safety of rituximab SC versus the IV formulation as part of a R-CHOP regimen. Patient satisfaction with treatment was also assessed| 151 centers | DLBCL (<i>n</i> = 576) | 1) R-CHOP with rituximab SC  2) R-CHOP with rituximab IV | – |

<sup>a</sup> Twenty cases and 33 patients were included. Changes in drug costs and resource use were analyzed. 
<sup>b</sup> In the first year of treatment. 
<sup>c</sup> At the start of the study. 
<sup>d</sup> For Rituximab SC.
| Publication | Country | Study design and aim | Data source | Patient population and intervention | Cost outcomes identified | Time/resource-use outcomes identified |
|-------------|---------|----------------------|-------------|-------------------------------------|--------------------------|--------------------------------------|
| Mihajlovic 2017 [90] | The Netherlands | Prospective, observational, bottom-up micro costing study to identify and compare all direct costs of intravenous and subcutaneous rituximab given to patients with diffuse large B-cell lymphoma in the Netherlands | Isala Clinics, Medical Center Leeuwarden (MCL), AZC Dordrecht, MCAI-kmaar, OMC Sittard-Geleen, Maasstad Hospital | DLBCL (NR) 1) Rituximab SC 2) Rituximab IV | Total direct cost saving €265.17 (€2176.77 versus €1911.09) | Nursing: 16.5 versus 13.7 min  Pharmacy: 4.0 versus 3.7 min, 16 s shorter for SC |
| Fargier 2018 [91] | France | Observational cross-sectional to evaluate the economic impact of using SC rituximab as maintenance therapy compared with usual patient care for follicular lymphoma, and to investigate HRQoL, patients’ and nurses’ perceptions and preferences, in the context of the French health service | Three teaching hospitals in Lyon, Nantes, and Tours | Follicular lymphoma (n = 73) 1) Rituximab IV 2) Rituximab SC | Direct costs, €1897.40 versus €1788.10/cycle  Cost difference of €109.20  Rituximab €1863 versus €1777  Pre-medication, €1.10 versus €0.20  Consumables, €21 versus £0.51  Active HCP time, €21.90 versus £9.90 | Pharmacist, 9.1 versus 3.5 min  Nurse, 23.7 versus 11.8 min |
| Rule 2014 [92] | UK | Prospective, observational, time-and-motion study to investigate the staff time and costs associated with administration of SC and IV rituximab | Plymouth, London, Oxford | NHL (n = 700) 1) Rituximab SC 2) Rituximab IV | Mean staff cost savings: £115.17 (£146.43 versus £31.26) £375.85 per course (5 sessions per year) | Treatment room time, 264 versus 70 min  Hospital time, 304 versus 110 min  Total HCP, 223 versus 48.5 min, saving 174.8 min per infusion  Chair time, 239 versus 46 min, 193.1 min saving per infusion |
| Ben Lakhal 2019 [93] | Tunisia | Cost-minimization analysis and budget impact model to evaluate cost and time/resource use impact associated with the administration of rituximab SC and IV administrations on the Tunisian health system over 3 years | Hospital Aziza Othmana | B NHL (NR) 1) Rituximab SC 2) Rituximab IV | TND 545 versus TND 330 per patient | Annual saving of nursing time, 22.13 days  Chair time annual saving, 193.5 days |
| Chansung 2018 [94] | Thailand | Randomized controlled trial to evaluate preference, satisfaction of patients, efficacy and economic burden between rituximab IV versus rituximab SC | NR | DLBCL and FL (n = 30) 1) Rituximab SC 2) Rituximab IV | Productivity loss THB 291.28 versus 8.66 | Infusion time, 212.4 versus 6.3 min |
| Publication | Study country | Study design and aim | Data source | Patient population and intervention | Cost outcomes identified | Time/resource-use outcomes identified |
|-------------|---------------|----------------------|-------------|-------------------------------------|--------------------------|---------------------------------------|
| Delgado-Sánchez 2019 [95] Spain | Retrospective study to compare the direct costs associated with the use of IV and SC rituximab, not only considering the drug price but also the costs of pharmacy handling, place occupation and administration in the day care unit. To determine whether the results could be modified with the availability of the new IV biosimilar of rituximab and develop an exploratory analysis in a nonlymphoma group | Son Espases University Hospital, the third-level reference hospital of Balearic Islands (database of the Pharmacy Department, Oncosafety®-AVIDA software) | Adult patients with lymphoma (n = 105) | Direct cost, €1955.94 versus €1460.01, saving of €495.93 (€1729 for IV biosimilar) | HCP time, day care unit time, 4 versus 1 h (standard practice times) |
| Di Rocco 2017 [96] Italy | Prospective study to evaluate the costs of the two different formulations of rituximab (IV versus SC) combined with CHOP and the efficacy in terms of complete response rates and toxicity | Department of Cellular Biotechnologies and Haematology, University of Rome Sapienza | DLBCL (n = 71) | Direct costs, €472,227 versus €449,870 for 35 and 36 patients, respectively | Chair time, 240 versus 135 min |
| Fisher 2017 [97] USA | Prospective, observational, time-and-motion study to understanding the patient perspective regarding rituximab administration to make decisions between intravenous (IV) and SC methods of administration | NR | FL, DLBCL and CLL patients (n = 40) | – | Time at infusion center, 319 min Time in infusion chair, 212 min |
| Irwin 2017 [98] UK | Observational study to investigate cost savings and reduction in chair times for patients treated with chemotherapy regimens containing SC rituximab therapy compared to IV rituximab therapy in a single center in the UK | University Hospital of Wales | NHL and DLBCL (NR) | Rituximab maintenance: 150 versus 11 min (R-CHOP: 260 versus 130 min R-CVP: 135 versus 50 min) | – |
| Publication       | Study country | Study design and aim                                                                 | Data source                  | Patient population and intervention | Cost outcomes identified          | Time/resource-use outcomes identified |
|------------------|---------------|--------------------------------------------------------------------------------------|------------------------------|------------------------------------|-----------------------------------|---------------------------------------|
| Lebas 2018 [99]  | France        | Retrospective study to review the issues introduced by a switch from Rituximab (Mabthera®) to its biosimilar product and quantify what cost savings can be expecteda | Alpes Leman Hospital         | Patients who had been provided Rituximab (Mabthera) (n = 52) 1. Mabthera IV/SC 2. Truxima IV/SC | Annual hospital saving €49,372        | Annual total hospital infusion time saving 101 h |
| McBride 2018b [100] (linked with McBride 2018a [102]) | USA            | Economic model to perform a time and cost simulation of reference IV, SC, and biosimilar IV rituximab from the US payer perspectived | Simulation study             | NHL (NR) 1. Rituximab IV 2. Rituximab IV-S 3. Rituximab IV-R90 | Direct incremental costs: US$4261 higher if BSA, 1.62 m2 US$27 higher if BSA 1.85 m2 US$4,208 saving if BSA 2.1 m2 | Chair time, administration time saving 2 h 9 min–2 h 23 min per infusion versus standard IV infusion (depending on BSA) |
| McBride 2018c [101] | USA            | Economic model to conduct a time and cost simulation of RITUX single agent maintenance therapy for FL comparing SC RITUX, rRITUX, and bRITUX from the U.S. payer perspective following initiation therapyd | Simulation study             | FL (NR) 1. Rituximab SC 2. Rituximab IV-S 3. Rituximab IV-R90 | Direct costs savings over 2 years: US$1120–19,331 depending on BSA 1.62–2.1 m² | Chair time, administration time saving 2 h 10 min–2 h 24 min per infusion (depending on BSA) |
| McBride 2018a [102] (linked with McBride 2018b [100]) | USA            | Economic model to perform a time and cost simulation of SC RITUX, rRITUX and bRITUX from the US payer perspectived | Simulation study             | NHL (NR) 1. Rituximab SC 2. Rituximab IV-S 3. Rituximab IV-R90 | Direct costs savings of US$104–4012 depending on BSA (1.62–2.1 m²) | Chair time, administration time saving 2 h 10 min–2 h 24 min per infusion (depending on BSA) |
| Nikolov 2017 [103] | Macedonia      | Cost-minimization analysis to identify and compare the total costs of subcutaneous versus intravenous administration of rituximab for the treatment of NHL patients in the Republic of Macedoniaa | Stem Cell Transplantation Unit, Outpatient Clinic, Clinical Department, University Clinic of Hematology, Skopje | NHL (n = 220) 1. Rituximab SC 2. Rituximab IV | Total direct cost saving €75 (€1621 versus 1546) Savings: €12.86 for HCP time (€14.62 versus €1.76) €89 for chair occupying cost (€10.10 versus €1.20) | Chair time, 6 h 12 min versus 10 min |
| Tomarchio 2017 [104] | Italy          | Economic analysis to evaluate, in patients with DLBCL and FL, the economic and social impact of subcutaneous rituximab administrationa | NR                           | DLBCL and FL (n = 40) 1. Rituximab IV 2. Rituximab SC | Total direct cost saving £274.49 Drug cost saving £156.27 per patient | Patient time, total saving per eight-cycle course 17.5 h Nursing: 144 versus 111 min Pharmacy, 40 versus 19 min |
| Publication          | Study country       | Study design and aim                                                                 | Data source                                                                                   | Patient population and intervention                                                                 | Cost outcomes identified          | Time/resource-use outcomes identified |
|---------------------|---------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------|---------------------------------------|
| Chansung 2018b [106]| Thailand            | Retrospective study of rituximab SC and rituximab IV to investigate whether adopting rituximab SC would yield cost saving in payers’ perspective⁵ | CHI of Thailand; HER                                                                           | DLBCL (n = 1011) 1) Rituximab SC 2) Rituximab IV                                                | THB 562 saving per cycle          | –                                     |
| Annibali 2017 [107] | Italy               | Cross-sectional study to evaluate in DLBCL and FL the economic and social impact of SC Rituximab⁶ | NR                                                                                          | DLBCL (n = 45 patients; n = 45 caregivers) 1) Rituximab SC 2) Rituximab IV                        | €274.49/patient saving           | –                                     |
| Gomes 2017 [108]    | Brazil              | Economic analysis to compare the total cost of rituximab IV versus SC in both indications approved by ANVISA for rituximab SC: FL first line and maintenance and DLBCL first line⁷ | Hospital Geral de Curitiba                                                                  | FL and DLBCL patients (NR) 1) Rituximab SC 2) Rituximab IV                                       | Total savings:                   | –                                     |
|                     |                     |                                                                                    |                                                                                             |                                                                                                   | FL: 12,091.66 BRL DLBCL: 4454.82 BRL                                                            |                                      |                                      |
| Kashiura 2018b [109]| Brazil              | Economic analysis to estimate the budgetary impact of the introduction of subcutaneous rituximab, compared with intravenous rituximab, in the Brazilian Private Healthcare System, to treat diffuse large B-cell and follicular CD-20+ patients with NHL⁸ | Data from National Regulatory Agency for Private Health Insurance and Plans; data from Survey performed with 28 HMOs | NHL (n = 5783) 1) Rituximab SC 2) Rituximab IV                                                  | BIM, savings over 5 years,         | –                                     |
|                     |                     |                                                                                    |                                                                                             |                                                                                                   | 344.7 million BRL for large health maintenance organization, (0.4 million beneficiaries)       |                                      |                                      |
| Rauf 2017 [110]     | Kingdom of Saudi Arabia| Economic analysis to investigate the economic implications of using rituximab SC compared to IV formulation in KSA for NHL⁹ | Clinical and cost inputs were obtained through discussion with medical oncologists and hematologists; other data came from budget impact model | NHL (NR) 1) Mabthera IV 2) Mabthera SC                                                          | BIM, total budget reduction        | –                                     |
| Stewart 2018 [111]  | Canada              | Economic analysis to estimate the effect (on systemic therapy suite time and on the costs of drug acquisition and administration) of implementing SC rituximab in the initial chemosimmunotherapy for FL and DLBCL over 3 years in the Canadian market⁴ | Time-and-motion data from UK based study; key input parameters of the model were based on literature and chart review data; data outputs from authors’ model | FL and DLBCL (NR) 1) Rituximab SC 2) Rituximab IV                                         | BIM, over 3 years: 128.715 systemic therapy suite hours saved | –                                     |
|                     |                     |                                                                                    |                                                                                             |                                                                                                   | Approximately Can$40 million saved in drug and administration costs                             |                                      |                                      |
| Publication   | Study country | Study design and aim                                                                 | Data source                                  | Patient population and intervention                                                                 | Cost outcomes identified                                      | Time/resource-use outcomes identified |
|--------------|---------------|------------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|----------------------------------------|
| Cristiano 2017 [112] | Czech Republic | Cost analysis to assess denosumab versus zoledronic acid in the prevention of SREs in adults with bone metastases from prostate cancer, BC, and OST (excluding hematological malignancies) from a national payer perspective in the Czech Republicd | Unit cost inputs for the model taken from multiple sources | Prostate cancer, BC and patients with other solid tumors (NR) 1) Denosumab SC 2) Zoledronic acid IV | Denosumab SC, CZK186.20  Zoledronic acid IV, CZK409.17 | –                                      |
| Li 2019 [113] | China         | Randomized controlled trial to treat Chinese patients with malignant melanoma using a high dose of subcutaneous IFN-α or continuous intravenous IL-2 for 4 months. The secondary end point of the trial was to compare the efficacy and safety of IFN-α therapy with IL-2 therapy and to do the research that Chinese guidelines are inadequate when it comes to using of IFN-α as a cancer treatmenta | Cancer Hospital of China Medical University | Malignant melanoma (n = 250) 1) INF-α SC 2) Continuous IL-2 IV | Total direct cost/patient IFN-α SC, ¥105,345 IL-2 IV, ¥95,656; p < 0.0001 | –                                      |
| Raje 2018 [114] | USA           | Cost analysis to estimate the incremental cost ratio and the net monetary benefit of denosumab versus zoledronic acid in patients with MM, from the perspectives of both society and payers5 | Unit costs for the model taken from multiple sources | Multiple myeloma (NR) 1) Denosumab SC 2) Zoledronic acid IV | Denosumab SC administration, US$42.18  Zoledronic acid IV, US$184.17 US$ 2017 | –                                      |
| Publication       | Study country | Study design and aim                                                                 | Data source                                      | Patient population and intervention                                                                 | Cost outcomes identified       | Time/resource-use outcomes identified |
|------------------|---------------|--------------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------------|---------------------------------------|
| Stopeck 2012 [115] | USA           | Cost analysis to assess denosumab relative to zoledronic acid for the prevention of SREs among patients with bone metastases secondary to castration-resistant prostate cancer, BC, or non-small cell lung cancer, based on a lifetime Markov cohort model from a US managed care perspective. Authors aimed to obtain incremental cost ratios including cost per quality-adjusted life year gained and cost per SRE avoided. | Unit costs for the model taken from multiple source | Castration-resistant prostate cancer, BC, and non-small-cell lung cancer, and bone metastases (NR) 1) Denosumab SC 2) Zoledronic acid IV | Denosumab SC administration, US$35.42 Zoledronic acid IV administration, US$154.64 US$ 2011 | –                                    |
| Zhang 2018 [116] | Australia, Belgium, Brazil, Canada, Czech Republic, Germany, Hungary, Denmark, Italy, Spain, France, Great Britain, Greece, Israel, Japan, Korea, Mexico, The Netherlands, Turkey, Ukraine, Poland, Russia, Sweden, Taiwan, USA | Cost analysis of DvD, Vd (both including SC bortezomib) and DRd (all IV) in patients with RRMM using data from two phase 3 trials (CASTOR and POLLUX). Multiple centers across different countries | RRMM (n = 569 [POL-LUX]; n = 498 [CASTOR]) 1) Lenalidomide and dexamethasone 2) Lenalidomide, dexamethasone and daratumumab OR 1) Bortezomib and dexamethasone 2) Bortezomib, dexamethasone and daratumumab | Cost per administration: DRd: $134 DVD: $203 Vd: $69 | –                                    |
| Body 2017 [117] | Belgium, Germany, Italy | Observational time-and-motion study to estimate total task time and total active healthcare professional time for predefined tasks associated with denosumab and zoledronic acid monotherapy administration. Secondary objectives included estimating patient time in the DOU, time in the treatment unit, and time in the treatment chair or on the examination table. Ten day-oncology units across Belgium, Germany, and Italy | Bone metastases secondary to a solid tumor (n = 189) 1) Denosumab SC 2) Zoledronic acid IV | Zoledronic acid IV versus denosumab SC Total time per administration, 44.2 versus 8.4 min Administration time, 25.1 versus 1.5 min Active HCP time, 12.2 versus 6.9 min Chair time, 44.7 versus 7.3 min Treatment room time, 46.7 versus 12.3 min Patient time in hospital, 103 versus 69 min | –                                    |
| Publication                  | Study country                  | Study design and aim                                      | Data source                              | Patient population and intervention | Cost outcomes identified | Time/resource-use outcomes identified |
|-----------------------------|-------------------------------|----------------------------------------------------------|------------------------------------------|-------------------------------------|-------------------------|---------------------------------------|
| Despiau 2017 [118]         | France                        | Observational study to assess the consequences of this new route of administration on the organization of a day hospital in real conditions, at the oncology day hospital of the Toulouse University Cancer Institute Oncopole<sup>a</sup> | Institut universitaire du cancer Toulouse-Oncopole | Patients with cancer (n = 48) 1) SC 2) IV | –                       | Duration of outpatient stay, 1 h shorter for SC versus IV administration Reflects 82% decrease in treatment duration Waiting times before treatment did not differ |
| Other agents—abstracts     |                               |                                                          |                                          |                                     |                         |                                       |
| Mateos 2019 [119]          | Sweden, Poland, Czech Republic, Ukraine, Canada, UK, Japan, USA | Randomized, open-label, non-inferiority, phase 3 study. Study aim NR<sup>b</sup> | NR                                       | RRMM (n = 522) 1) Daratumumab SC 2) Daratumumab IV | –                       | Median duration for administration: IV: 421/255/205 min for the first/second/subsequent infusions SC: 5 min |

BIM budget impact model, BRL Brazilian real, BSA body surface area, CVAD, central venous access device; CHI, Center Office of Healthcare Information; CZK, Czech Republic Koruna; DLBCL, diffuse large B-cell lymphoma; DRd, daratumumab; DVd, bortezomib, daratumumab and dexamethasone; FL, follicular lymphoma; h hour, FTE full-time equivalents, HCP healthcare professional, HKD Hong Kong dollar, IFN-α interferon-alpha, IL-2 interleukin-2, IV intravenous, MBC metastatic breast cancer, MGC metastatic gastric cancer, min minute, NHL non-Hodgkin’s lymphoma, NHS National Health Service, NR not reported, NZD New Zealand dollar, R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, R-CVP, rituximab, cyclophosphamide, vincristine sulfate and prednisone, RCT z controlled trial, SC subcutaneous, SLR systematic literature review, THB Thai Bhat

<sup>a</sup>The perspective of this study was not explicitly stated in the publication

<sup>b</sup>This study was conducted from the societal perspective

<sup>c</sup>This study was conducted from the perspective of the UK NHS

<sup>d</sup>This study was conducted from the payer perspective

<sup>e</sup>This study was conducted from the US managed care perspective
3.3.2 Administration Time

Administration time for trastuzumab was reported in five publications, of which four directly measured time [49, 53, 54, 62]; one publication reported estimated time from drug delivery software [51], which was found to be consistent with the other four publications. Administration times of 90 and 30 min were reported for IV trastuzumab loading and subsequent doses, respectively, in two of the publications [51, 54]. A further two publications reported times of 38 and 97 min for IV trastuzumab administration [53, 62]. In contrast, the reported times for SC trastuzumab administration ranged from 5 to 10 min, with no difference between loading and subsequent doses. The differences in administration time between IV and SC were 80–85 (loading dose) and 20–25 min (subsequent doses) [51, 54], and 32–107 min in the three publications in which loading/subsequent doses were not specified [49, 53, 62]. Additionally, two publications reported time savings of 47 min [60] and 61 min [48] with SC trastuzumab, for combined preparation and administration times.

3.3.3 Active Healthcare Professional (HCP) Time

Active HCP time, and time savings with SC versus IV trastuzumab, were reported in nine publications and are shown in Fig. 3. Based on direct measurements, active HCP time was 13–92 min (IV) versus 7–30 min (SC); a difference of 6–62 min [50, 53, 59, 62–65, 67]. Two publications reported a longer administration time for the loading dose of IV trastuzumab (92 and 44 min); here, the time differences between the loading dose of IV and SC were 62 and 18 min [64, 65]. One publication reported only on the time difference (15 min) between IV and SC [57]. One other publication reported only the difference in HCP time (7 min), which was estimated based on drug preparation software [68]. One report of active HCP time included a range of 7–12 min (IV) versus 4–7 min (SC).
[55]; however, it is unclear what was included within the time, and why the HCP times in this report were shorter than those of other publications. Active time differences were also reported for different HCPs and were all in favor of SC versus IV administration: differences in nursing times were 6.1 min [62] and 10.6 min [59]; pharmacist and nursing assistant time differences were 3.0 min and 0.3 min, respectively [59]; and one publication reported time savings of 0.18 full-time equivalents (FTE) and 0.14 FTE with SC for nurses and pharmacists, respectively [56].

3.3.4 Patient Chair/Infusion Time

Chair time, where defined, was described consistently as the period between entry and exit from the infusion chair; however, how the time was determined varied between publications, with some reporting studies that measured the time directly [25, 50, 52, 55, 57–59, 62, 67, 68] and others reporting studies that estimated time from chemotherapy prescription software and HCP interviews [57, 68]. Differences in chair time for trastuzumab administration were reported in 10 publications [25, 50, 52, 55, 57–59, 62, 67, 68], of which seven reported actual chair times and differences obtained through direct measurement; one publication estimated the chair time based on drug delivery software [68] and was consistent with the other seven publications. Chair time was 47–180 min (IV) versus 8–120 min (SC); the difference in time was 33–126 min (Fig. 4). One publication reported a sixfold decrease in chair time with SC administration [58], with another describing a 56% reduction [52]. The PrefHer time-and-motion study reported chair time differences from nine countries (Fig. 5), ranging from a difference of 47.1 min (Denmark) to 85.5 min (Spain) for administration with the single-use injection device and 40.3 min (Italy) to 80.6 min (Spain) for administration with a hand-held syringe [25].

Total time spent at the hospital was also reported, ranging from 3–7 h (IV) to 1–5 h (SC), with a difference of 1.5–2 h [59, 64, 67]. One publication reported the difference for subsequent doses (following the loading dose) to be lower (23-min difference: 90 min IV vs. 67 min SC) [64].

3.4 Costs Associated with IV Versus SC Administration of Trastuzumab

Costs for IV versus SC administration of trastuzumab were gathered from 24 publications with sufficient level of detail to show how the costs were defined. Costs were reported per administration, per treatment course, per patient per year, or for a particular cohort. Of these 24 publications, 18 reported costs based on data from time-and-motion studies or studies in which the time for specific procedures was directly measured; one based estimates on information provided by drug preparation/administration software [51], one estimated time from a survey of HCPs [70], and four did not report how time was estimated [56, 69, 82, 83]. Twelve of the publications were full publications, with the other 12 being congress abstracts with limited detail (Fig. 2).

Thirteen publications covering ten countries reported total direct medical costs for IV versus SC administration [51, 53, 54, 59, 60, 63, 64, 69, 82–86], which included non-drug costs for preparation, administration, HCP time and consumables, and savings related to reduced drug wastage or administered dose. All but four publications [51, 69, 82, 83] indicated that time assessments were made directly. Cost savings for SC compared with IV administration were reported in all but one publication, which reported data from a study conducted in Italy that used time estimates from drug delivery software rather than direct time assessments [51]. In this publication, total costs were numerically greater for SC administration; however, the difference was not statistically significant and was likely related to differences in drug acquisition costs as preparation and day hospital costs were shown to be significantly lower for SC administration [51].

In seven of the publications, direct costs for SC administration were approximately 1.3–6% lower than those for IV administration. One publication from a Russian study reported a 12.6% decrease [83] and one from the UK reported a 2.8-fold decrease [85] in direct costs with SC
versus IV administration. Twelve publications provided information on costs directly related to active HCP time, preparation and/or administration time, patients’ time, or chair time [50, 53, 54, 56, 59, 62–65, 67, 84, 85]. All reported reduced time-related costs with SC versus IV administration.

In the five publications reporting total costs including indirect costs, indirect costs were lower for patients who received SC versus IV trastuzumab [51, 59, 63, 64, 71]. SC administration costs were also lower for consumables [49, 53, 54, 57, 59, 61–64, 67], drug wastage [67], use of central venous access devices [86], overheads [87], nursing and pharmacy supplies [84], and avoiding catheter implantation surgeries [54] compared with administration costs for IV in all publications that reported such information. One publication reported non-drug costs for the first and for subsequent cycles of therapy; reported costs were higher for the first cycle of therapy for both SC and IV administration [65]. One publication reported the costs for management of adverse events, which were slightly higher for SC versus IV delivery (US$1574 vs. US$1715 for 18 cycles) [71].

In addition to the 24 publications reporting cost-related data, five further publications were identified that reported on the budget impact of introducing SC trastuzumab; all reported cost savings across varying time periods [69, 72–75].

### 3.5 Time/Resource Use with IV Versus SC Administration of Rituximab

Nineteen publications (seven full publications [52, 66, 88–92] and 12 abstracts [93–104]) reported data on time required, or differences in time required, for IV versus SC rituximab for the treatment of lymphoma (NHL/FL or DLBCL in most publications) (Fig. 2). Of these, 12 reported data from time-and-motion studies or studies in which the time for specific procedures was directly measured, two estimated time from a survey of HCPs [66, 93], and five did not report how time was estimated [52, 89, 101].

#### 3.5.1 Preparation Time

Preparation time or pharmacist time per infusion of rituximab was reported in five publications and ranged from 4–40 min (IV) to 2–20 min (SC) [66, 88, 90, 91, 104]. One of these publications reported a study that collected relevant data using a survey [66]; however, data were consistent with those estimated from direct measurement. In all publications, preparation/pharmacist time was shorter for SC administration, with time savings of 5.6–21 min (in one publication there was a marginal difference of 0.3 min [90]).
3.5.2 Active HCP Time

Differences in HCP time per infusion of rituximab were reported in five publications and directly measured [88, 90–92, 104]. HCP times were 17–35 min (IV) compared with 12–24 min (SC) in three publications, whereas two publications reported longer times of 144 and 223 min (IV) versus 111 and 49 min (SC). All five publications found that SC administration was associated with a time saving. A further publication reported annual savings of nurse time to be 22 days for a single center in Tunisia [93] and one reported a time saving of 3 h in the day-care unit per infusion [95].

3.5.3 Patient Chair/Infusion Time

Chair time/infusion time for rituximab was reported in ten publications [88, 89, 92, 94, 96, 98, 100–103] and one further publication reported the time for IV administration [97]. For four of these publications, the method of time assessment was not reported; the remaining publications used direct time measurements. Chair time/infusion time was considerably shorter for SC versus IV administration in all publications, ranging from 150–262 min (IV; one publication reported a time of 6 h and 12 min (372 min)) to 6–11 min (46 and 135 min in two publications) for SC administration. Time saved with SC administration ranged from 1 h 45 min to 3 h 26 min (a saving of 6 h in one publication with a particularly long time for IV administration). A 74% reduction in chair time with SC administration was reported in another publication [52], and annual time savings per center of 101 h [99] and 193.5 days (administration time estimated using a survey) [93] were also reported. Time spent in the treatment room was directly measured and ranged from 264–321 min (IV) to 70–105 min (SC). Time savings with SC administration were ~200 min [66, 88, 92, 97]. One publication reported a time saving of 17.5 h per eight-cycle course of treatment [104].

3.6 Costs Associated with IV Versus SC Administration of Rituximab

Costs for management of patients with NHL/FL or DLBCL receiving IV versus SC administration of rituximab were gathered from 18 publications. Of these, 11 reported costs based on direct assessment of HCP time, one estimated time from a survey of HCPs [93], and six did not report how time was estimated [100–102, 105–107]. Only three of the publications were full papers; the rest were congress abstracts (Fig. 2). Three simulation analysis study publications conducted in the USA report cost savings for SC versus IV administration incrementally according to patient body surface area [100–102], which is used to calculate the IV dose (the SC dose is fixed). One publication reporting costs for rituximab maintenance therapy for FL over 2 years [101] and one publication reporting costs of rituximab as part of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy (R-CHOP) for patients with NHL [102] reported higher cost savings for patients with higher body surface area (BSA). The other publication, which also reported costs of rituximab as part of R-CHOP therapy for NHL, reported the highest cost savings for patients in the highest and lowest BSA categories, respectively [100]. However, the reason for this discrepancy is unclear. Reductions in direct medical costs for SC versus IV administration were reported in all nine of the publications reporting European studies, all but one [107] of which estimated time savings based on direct measurements, and in four additional publications of studies from Tunisia (time savings estimated by HCP survey) [93], Thailand [94, 106], and Brazil [108]. In the European publications, non-drug-related cost savings included savings related to HCP time [53, 91, 92, 103], consumables [53, 91], and day-care unit costs [53, 95]. One of the publications from Thailand, which reported societal costs, reported a reduction in productivity loss with SC versus IV administration [94]. A further three congress abstracts describing the budget impact of introducing SC rituximab in Brazil, Saudi Arabia, and Canada were identified, all of which reported cost savings at 1, 2, 3, or 5 years [109–111].

3.7 Other Publications

In addition to the publications regarding trastuzumab and rituximab, eight other publications were identified that report relative time or cost information for IV versus SC administration (Table 2) [112–119]:

- Three of four cost analysis publications were considered less relevant as they reported time and cost of supportive therapies (SC-administered denosumab vs. IV-administered zoledronic acid) rather than treatment with a targeted oncology drug [112, 114, 115]. The remaining cost analysis publication reported higher administration costs for the regimens containing SC bortezomib, daratumumab, and dexamethasone than for those containing daratumumab, lenalidomide, and dexamethasone (all IV) in patients with relapsed/refractory multiple myeloma from two Phase III clinical trials [116].
- One publication from a randomized controlled trial at a single Chinese hospital reported significantly (p < 0.0001) lower direct costs per patient for high-dose SC interferon-alpha compared with continuous IV interleukin-2 administration in patients with malignant myeloma [113].
- Three publications reported directly measured time assessments for various oncology therapies; all of these
4 Discussion

4.1 Interpretation of Results

Global increases in yearly cancer rates have resulted in increased numbers of IV infusions of chemotherapies and anticancer biologics. This represents a growing burden for medical centers and HCPs, and has led to a shortage of chair time for patients with cancer. The substantially shorter administration times of therapies administered subcutaneously has the potential to offer several advantages over IV administration, including shorter treatment times, a reduction in healthcare resource use, increased convenience for patients, and greater patient preference [25, 39, 40, 120].

In this SLR, we identified 72 publications reporting on the time/resource use and/or costs associated with IV versus SC administration of oncology biologics in a hospital setting or on the budget impact of introducing an SC formulation. The majority of reported publications were of studies conducted in single countries or even single centers; all studies were published between 2012 and 2020.

Overall, the results were largely consistent in demonstrating the time savings associated with preparation and administration of SC therapies, across both oncology biologics and other supportive therapies. Moreover, reductions were seen in the HCP time and resource use (including non-drug consumables and drug wastage) required for SC versus IV therapy administration. Patient hospital time was also shorter with SC versus IV administration, and additional cost savings may be achieved at the society level due to a reduction in the loss of productivity and leisure time associated with patients attending the hospital for treatment. However, these improvements in patient productivity are likely to be greater in patients receiving maintenance therapy than those receiving SC-administered oncology biologics in combination with chemotherapy, due to the increased patient chair time required for chemotherapy administration. Cost savings due to reduced production and leisure time loss for SC versus IV trastuzumab across five Swedish oncology clinics were €78 and €62, respectively, for first-time patients and €10 and €6, respectively, for subsequent patients [64]. Similarly, a study conducted in six hospitals in the Netherlands reported lower societal costs (travel expenses and costs related to informal care and loss of productivity) for SC versus IV administration for both trastuzumab (cost saving of €22) and rituximab (cost saving of €28) [53].

There was some variation in times reported for IV and SC preparation and administration of trastuzumab, which may reflect differences in time estimate methodologies, definitions of time periods, and clinical practice/hospital setup between the different participating centers. Notably, the multinational PrefHer time-and-motion study reported time differences between countries [25], despite presumably using similar definitions for each time period across the different centers involved in the study. Similar variations were also seen with studies of rituximab [88]; however, a consistent trend in favor of SC administration was observed across all publications. During the COVID-19 pandemic, urgent cancer referrals and chemotherapy attendances declined by up to 84.3% and 63.4%, respectively, which might have resulted in increased mortality rates in patients with cancer and multimorbidity [121]. The time savings of SC administration have the potential to help increase throughput of patients now that cancer services have resumed. In addition to this, decreased hospital time for patients with cancer may help to reduce the risk of COVID-19 infection and the associated high probability of mortality in these patients [122].

As expected, there were also variations in costs for IV and SC administration between publications that could be compared based on use of the same currency. However, six European publications reported similar percentage savings in direct costs and most publications showed a trend for cost savings with SC versus IV administration of trastuzumab. Two of the rituximab publications that showed cost differences for the SC and IV formulations incrementally based on BSA reported that the largest cost savings occurred for patients with higher BSA.

The findings of this SLR are consistent with other published SLRs that have reported on the time, resource, and cost savings associated with SC administration versus IV, for both oncology and non-oncology biologics [123–125]. However, cost reductions associated with time savings for HCPs may be difficult to measure and achieve in clinical practice [126]. Therefore, methods of improving the transferability of time-related cost savings to the clinic should be investigated.

The purpose of this SLR was to ultimately inform economic modeling and associated health technology assessment of PH FDC SC. Recommendations for durations of post-administration surveillance for SC and IV trastuzumab are identical, with 6 h of observation recommended after the first dose and 2 h of observation for all subsequent doses [42, 127–129]. Within the context of this SLR, observation times for SC and IV cancel out (as they are the same). The efficacy and safety profiles of SC and IV trastuzumab were also assumed to be comparable in this study. However, real-world evidence suggests that target levels of trastuzumab may not be reached with the first SC administration in patients with a high body weight and, although cardiotoxicity risk does not appear to be increased in patients with low body weight, Phase III trials have reported higher rates of adverse events with SC vs. IV administration [130].

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It is important to note that the focus of this SLR was on administration in the hospital setting only. However, similar to the benefits provided by other SC-administered oncology biologics [131–133], PH FDC SC is expected to offer advantages with regard to reduced time/resource utilization, improved patient quality of life, and the potential to be used in the future in a flexible care setting [43]. There is considerable evidence demonstrating that PH FDC SC is well suited to at-home administration by a HCP [134]. Providing at-home administration requires planning, training, careful patient selection and technology to link patients, caregivers, and specialists in oncology clinics, as well as innovative methods for treatment delivery (e.g., mobile care units) [134]. A US expanded access study (NCT04395508) investigating at-home administration of PH FDC SC by a home health nursing provider is ongoing. This study focuses on patients with HER2-positive breast cancer previously treated with IV pertuzumab plus trastuzumab and chemotherapy and currently receiving or due to receive maintenance therapy with pertuzumab plus trastuzumab alone.

4.2 Strengths and Limitations

One strength of this SLR is that it identified studies with a range of designs, although some were described only as economic analyses with no additional clearly defined design details included. The inclusion of both clinical trials and studies conducted in the real-world setting suggests that the reported time and cost savings may be translated to SC versus IV oncology biologics administered during standard clinical practice. The publications included in this SLR also reported several different methodologies for time assessments; however, results from the two studies that reported time estimates from drug delivery software or based on HCP surveys were largely consistent with those from studies that used direct measurements from time-and-motion-type methodologies.

Although the majority of the trastuzumab and rituximab studies identified were performed in European countries, full-text publications were identified for studies conducted in Canada, Chile, China, New Zealand, and the USA, and abstracts identified for studies conducted in Ecuador, Hong Kong, Japan, Mexico, Panama, Singapore, Thailand, Tunisia, and Saudi Arabia. Despite the potentially limited generalizability of the conclusions due to country-specific differences in approaches to healthcare, the consistency of the evidence supporting SC-related time and cost savings compared with IV administration presented in this SLR suggest that the findings are likely to be applicable across different healthcare systems and countries.

Due to the large number of potentially relevant publications comparing SC with IV administration, the decision was made to focus the literature search on anticancer drugs. Although this pragmatic approach could lead to relevant data/insights being missed, the oncology publications included in this SLR can offer a chance of providing valuable insights into the impact of the route of administration on treatment costs.

The focus of this SLR was to identify potential time differences associated with SC versus IV administration, as well as differences in non-time-related cost elements such as non-drug consumables. As a result, the drug costs of the treatments being administered were not considered. However, it is important to acknowledge the need for decision makers to take a holistic approach to healthcare resource utilization, which accounts for both drug and non-drug costs, in order to ensure optimal management of resources.

In the future, more studies should address the economic benefits for different institutions of patients switching from IV to SC oncology biologics [54], rather than simply comparing different patient populations treated via either IV or SC administration. Furthermore, as the current economic assessments have mainly been performed in developed countries and there are concerns about the transferability of SC versus IV benefits to less developed countries [126], more studies should be conducted in regions such as Eastern Europe or Latin America to assess the applicability of our findings there.

5 Conclusion

This SLR indicates that there is a substantial body of evidence demonstrating oncology biologics administered by the SC route in a hospital setting to be associated with important time and resource use savings versus IV administration. The identified evidence provides valuable inputs for economic evaluations of PH FDC SC, or for other SC oncology treatments.

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Declarations

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