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ORIGINAL ARTICLE

# Rationale and budget impact of bimonthly use of Cetuximab in patients with recurrent and/or metastatic head and neck cancer

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**Abstract**

**Background:** In recurrent and/or metastatic head and neck squamous cell cancer, Cetuximab is administered once a week, followed by weekly doses. We present the clinical rationale of a different schedule of maintenance Cetuximab and we estimate the potential economic benefits on the health care budget from a societal perspective in Italy.

**Methods:** A budget impact (BI) excel-based model was developed comparing a base case scenario of 100% weekly administration with a dose of 250 mg/m$^2$ to an every-other-week (EOW) administration at 50% or 100% with a dose of 500 mg/m$^2$.

**Results:** In the EOW, 50% scenario it was calculated a cost reduction of €347 000 of which 70% attributable to indirect costs, increasing to €694 000 after 4 months.

**Conclusions:** In our analysis, we showed that this simplified schedule could also reduce the costs of treatments both for the health system (direct costs) and for the society (indirect costs).

KEYWORDS

budget, cetuximab, economic benefits, every-other week, head and neck cancer

## 1 | INTRODUCTION

Cetuximab is a chimeric monoclonal immunoglobulin $G_1$ antibody inhibitor of the epidermal growth factor receptor. Because of the substantial benefit in progression-free survival (PFS) and overall survival (OS),[1,2] Cetuximab is indicated for the treatment of head and neck squamous cell cancer (HNSCC) both in combination with radiotherapy for locally advanced disease and with platinum-based chemotherapy for recurrent and/or metastatic (RM) disease. In all indications, Cetuximab is administered by intravenous infusion once a week at an initial dose of 400 mg/m$^2$, followed by weekly doses of 250 mg/m$^2$.[3] Although the weekly schedule was validated in clinical studies, the long Cetuximab half-life of 66-98 hours makes its administration every other week (EOW) theoretically possible.

Pharmacodynamic (PD) and pharmacokinetic (PK) studies have demonstrated the bioequivalence as well as the efficacy of a EOW dosing schedule, when Cetuximab was used as a treatment of colorectal cancer.[4–7] Some studies in HNSCC, limited to the setting of RM disease, demonstrated a similar profile of toxicities and activity when Cetuximab was used with an EOW therapeutic schedule. In Italy, Cetuximab can be administered alone and EOW in the maintenance phase after completion of platinum-based and Cetuximab first-line treatment.[6,8] Therefore, the benefits of an EOW administration would rely on the greater compliance of the patients when the treatment is in maintenance phase and extends over time.

As of today, the clinical rationale for the adoption of an EOW administration has not been investigated together with the economic consequences on the health care system. In particular, due to the scarcity of data in the literature, the budget impact (BI) of an EOW administration schedule for Cetuximab has not been assessed from the perspective of the health care service in Italy.

The objective of the present analysis is to present the clinical rationale of a different administration method of

  

Cetuximab in patients diagnosed with RM HNSCC together with the economic analysis and the estimation of the potential economic benefits on the health care budget.

## 2 | RATIONALE

### 2.1 | PK and PD data

PK and PD for the standard weekly Cetuximab and EOW regimens were evaluated in a phase I study performed in 62 patients with metastatic colorectal cancer.[5] The study was in two parts: a 6-week Cetuximab monotherapy dose-escalation phase and a subsequent combination-therapy phase, during which patients received Cetuximab at the same dose/schedule as in the monotherapy phase, combined with chemotherapy. Patients in the control group received Cetuximab at a 400 mg/m$^2$ initial dose, then 250 mg/m$^2$ each week, whereas patients assigned to the dose-escalation group after the initial Cetuximab infusion, received 400-700 mg/m$^2$ EOW. The PK analysis of the different treatment groups revealed that the 700 mg/m$^2$ EOW schedule deviated substantially from the other dose regimens, with higher trough concentrations in conjunction with delayed steady-state conditions, prolonged half-life, and reduced clearance. By contrast, trough concentration values for the 500 and 600 mg/m$^2$ EOW dosing regimen were comparable to the standard weekly regimen. Cetuximab serum concentrations and exposure increased with dose. The PK parameters terminal half-life, total plasma clearance and volume of distribution at steady state were comparable between the standard weekly and EOW 400, 500, and 600 mg/m$^2$ dosing regimens. In terms of exposure, the EOW 500 mg/m$^2$ dosing regimen matched more similarly the exposure of the 250 mg/m$^2$ weekly schedule. Based on these data, the authors concluded that, on the whole, the closest PK match to the weekly standard regimen was provided by EOW administration of 500 or 600 mg/m$^2$, with 500 mg/m$^2$ being the dose of choice in terms of convenience and feasibility. Moreover, functional data derived from immunohistochemical analysis of skin biopsies added to the PK analysis and provided a biologic rationale supporting the functional equivalence of the Cetuximab weekly and EOW dosing regimens.

### 2.2 | Clinical data

The safety of the EOW regimen of Cetuximab in RM HNSCC was investigated in a phase II study performed in patients with not more than two prior cytotoxic chemotherapy regimens, randomized to receive Cetuximab EOW at 500 mg/m$^2$ ($n = 35$) or 750 mg/m$^2$ ($n = 26$) until disease progression.[9] Escalating the dose to 750 mg/m$^2$ did not appear to offer any obvious therapeutic advantage; therefore, this arm was prematurely closed. The administration of 500 mg/m$^2$ EOW Cetuximab monotherapy was associated with grade 3/4 adverse events (AEs) in 48.6% of patients. Acneiform rash was the most common grade 3 toxicity (11%). This finding resembles the incidence of skin toxicity reported in previous studies of standard weekly dosing of Cetuximab, such as the EXTREME study, where grade 3 or higher skin reactions were reported in 9%.[2] Globally, the overall response rate (ORR) was 11.4% among the 35 RM HNSCC patients enrolled in this study and the median PFS and OS were 2.2 and 7.0 months, respectively.

In the maintenance setting, the EOW administration of Cetuximab 500 mg/m$^2$ was investigated in 31 RM HNSCC patients after chemotherapy plus weekly Cetuximab as first-line treatment.[10] The safety of maintenance treatment with EOW Cetuximab was evaluated and compared with the occurrence of AEs during the previous combination therapy (chemotherapy plus weekly Cetuximab). The rate of any grade 3/4 AEs was 45% and 29% in the two groups (EOW Cetuximab vs chemotherapy plus Cetuximab, respectively), whereas 16% and 19% of patients experienced grade 3/4 skin rash. In this analysis, EOW Cetuximab seemed to be well tolerated and most toxicities decreased with time during Cetuximab maintenance compared with combination therapy. No infusion reaction was observed with EOW Cetuximab at a dose of 500 mg/m$^2$.

The administration of Cetuximab and Docetaxel every 2 weeks as first-line treatment of RM HNSCC was analyzed in a retrospective series of 31 patients.[11] The Authors showed that grade 3/4 AEs were present in 67.7% of the patients, mainly consisting of neutropenia, hypomagnesemia, and skin rash, whereas ORR was 12.9% and median OS and PFS were 8.3 and 4 months, respectively.

The role of Cetuximab EOW as maintenance therapy was also investigated by Guigay et al.[12] who have evaluated the efficacy and safety of four cycles of Docetaxel associated with Cisplatin and Cetuximab (TPEx) as first-line treatment, followed by maintenance with Cetuximab every 2 weeks in patients with RM HNSCC. Fifty-four patients were enrolled, with the most common grade 3/4 AEs being skin rash (16.6%) and nonfebrile neutropenia (20.4%). The primary end point was met with an ORR of 44.4%; median OS and PFS were 14 and 6.2 months, respectively.

An observational French study prospectively evaluated a series of 72 patients receiving Cetuximab maintenance therapy, which was administered weekly or EOW at physician's discretion.[13] Grade 3/4 skin toxicities were observed in 7.6% of the patients, whereas interestingly the 12-month PFS rate and 12-month OS rate did not differ between patients treated every 2 weeks or weekly.

Feasibility of 6 months maintenance Cetuximab after adjuvant concurrent chemoradiation plus Cetuximab in HNSCC has also been evaluated by Matuschek et al.[14] Maintenance Cetuximab started after completion of chemoradiation therapy plus Cetuximab with 500 mg/m$^2$ every 2 weeks over a 6-month period. Compliance to maintenance

**TABLE 1** Epidemiological parameters to identify the population diagnosed with RM HNSCC treated with Cetuximab - Italy 2017

| Epidemiologic parameters | Model parameter (%) | Estimated population | Sources |
|---|---|---|---|
| Residential population | | 60 589 445 | 22 |
| HNSCC incidence | 0.015% | 9300 | 19 |
| Population with RM HNSCC | 45.0% | 4185 | 20 |
| Patients treated with Cetuximab | 32.3% | 1352 | 21 |
| Patients undergoing treatment with Cetuximab in maintenance phase after chemotherapy | 45.0% | 609 | 2 |

RM HNSCC, recurrent and/or metastatic head and neck squamous cell cancer.

Cetuximab was quite satisfactory: 80% were still on Cetuximab after 3 months and 63% after 5 months; 48% completed 6 months maintenance therapy.

## 3 | ECONOMIC CONSEQUENCES

An excel-based model was developed to estimate the potential economic benefits of EOW compared to weekly administration of Cetuximab among patients with RM HNSCC. A review of the epidemiological and economic literature was conducted to identify relevant information to include in the analysis. The model was then implemented following the guidelines suggested by the *International Society of Pharmacoeconomics and Outcomes Research* (ISPOR).[15,16]

### 3.1 | Comparison scenarios

In coherence with the current administration schedule, a base case scenario was set considering 100% of patients being treated with a weekly administration of Cetuximab.[17] In the comparison scenario, the base case administration was replaced with EOW administration at 50% or 100% for the maintenance therapy only. Specifically, in the base case scenario, the schedule included a dose of 250 mg/body surface area (BSA)[17] compared with one dose of 500 mg/BSA every 2 weeks (alternative scenario).

Moreover, the expense simulations have been broken down in cost analyses per milligram of drug used (base case) and per required ampoule (sensitivity analysis). The model assumed an average BSA of 1.8 $m^2$.[18] Details on the treatment schedules are reported in Table 2.

### 3.2 | Epidemiological parameters

As a first step, the size of the eligible population was identified from the national perspective according to the therapeutic indication in Italy. As reported in Table 1, incidence rates provided by the Italian Association of Cancer Registries[19] were used to estimate the cohort of individuals annually diagnosed with HNSCC cancer. Moreover, it was estimated that about 45% of these patients were diagnosed with RM disease.[20]

Being the model focused on patients treated with Cetuximab alone in the maintenance setting, we assumed that about 32% of patients were treated with first line platinum-based chemotherapy plus Cetuximab[21] and that the portion undergoing Cetuximab monotherapy in maintenance phase was 45%.[2] As a result, the model estimated a cohort of patients treated with Cetuximab equivalent to 609 patients a year (Table 1).[2]

The second step concerned the definition of the time horizon to consider in the analysis. Because of the limited PFS of RM HNSCC, we set a 2- to 4-month therapy time horizon.

### 3.3 | Cost parameters

With reference to the estimation of drug cost, the price of Cetuximab has been used net of discounts by law and according to the dosing of the two treatment schedules (Table 2). The model considered both the cost/mg and the cost/ampoule, according to the treatment schedules and the ampoules required for an average BSA of 1.8 $m^2$.

Furthermore, the cost associated with patients' management was estimated. According to this approach, the cost of medical examinations required for drug administration and patient management was included in addition to the indirect costs associated with the loss of productivity (absence from work) of the patient or caregiver.

Specifically, the model assumed a cost of €85/medical examination for each administration, including the cost of the physician, nurse, consumption material, for the drug administration, and distribution by the hospital pharmacy.[23]

**TABLE 2** Parameters of patient definition and therapy cost

| Parameters of patient definition H&N R/M | Parameter | Source |
|---|---|---|
| BSA patient, $m^2$ | 1.8 | 18 |
| Weekly ampoule CET_weekly/250 mg/BSA | 5.0/450 mg | 17 |
| Weekly ampoule CET_EOW/500 mg/BSA | 9.0/900 mg | Assumption |
| Number of lost working days/medical examination | 1.0 | Assumption |
| Cost parameters | Cost | Source |
| Ampoule price 100 mg | € 153.6 | AIFA |
| Cost of medical examination/ administration | € 85.0 | 23 |
| Cost of working day Italy | € 200.2 | 24,25 |

BSA, body surface area; CET, Cetuximab; EOW, every other week.

**TABLE 3** Budget impact results, base case vs EOW 50% scenario, 2 months

| | Expense | | |
|---|---|---|---|
| **Cost items** | **Base case (€)** | **EOW 50% scenario (€)** | **Budget impact (€)** |
| Drug cost (calculation/mg) | € 2 990 322 | € 2 990 322 | € 0 |
| Management cost/ administration | € 413 808 | € 310 356 | −€ 103 452 |
| Indirect costs | € 974 445 | € 730 833 | −€ 243 611 |
| Total expense | € 4 378 574 | € 4 031 511 | −€ 347 063 |
| | 1 week | EOW 50% scenario | Tot. no. of treated patients |
| Base case treated patients | 609 | 0 | 609 |
| 50% treated patients scenario | 304 | 304 | 609 |

With reference to the indirect costs, the model assumed the loss of a working day every time the drug is administered to the patient in the hospital setting. Such assumption was based on the hypothesis that, when drug is administered, the whole working day is lost either by the patient or the caregiver. Calculations were made considering an average salary/hour of €27.8[24] that corresponded to a daily salary of €200.2[24,25] before tax (Table 2).

Finally, the model does not consider efficacy and safety differences between the two schedules.

### 3.4 | Sensitivity analysis

Deterministic one-way sensitivity analysis was performed to model the uncertainty of the parameters and the consequent variability of the results. Following this approach, the results of the BI model have been obtained by varying one parameter of the model at once, depending on the variability observed in the literature or assumed by the authors. Specifically, the following scenarios have been considered:

- RM-HNSCC patients with maintenance treatment with Cetuximab (base case = 45.0%): Min = 35%-Max = 55%
- Cost of estimated drug by number of ampoules required for the administration (base case = cost/mg)
- Working days lost/visit (base case = 1 day lost): Min = 0-Max = 2

## 4 | RESULTS

The model estimated a total of 609 patients diagnosed with RM-HNSCC and subjected to treatment with Cetuximab once a week in the base case scenario. In the next paragraphs, the comparison between the base case and an EOW administration schedule applied to 50% and 100% of the eligible population is illustrated.

### 4.1 | Base case vs EOW 50% scenario

Table 3 illustrates the results in terms of BI after 2 months, considering 609 weekly treated patients vs 304 weekly patients and 304 bi-monthly treated patients. Considering an average BSA of 1.8 $m^2$, the two strategies (weekly administration of 250 mg/BSA vs EOW 500 mg/BSA) did not differ in terms of the cost of the drug/month. The model estimated a cost reduction of €347 000, of which over 70% was attributable to indirect costs. Administration costs showed a smaller saving of approximately €243 000 (Figure 1). In addition, the model estimated that, after 4 months of treatment, the cost reduction would increase to €694 000.

### 4.2 | Base case vs EOW 100% scenario

In this scenario, the BI of EOW strategy was compared with a weekly strategy for patients with RM-HNSCC at 2 and 4 months considering same drug expense for the two treatment strategies. As a result, the model estimated a cost reduction of €694 000, of which about 70% is due to indirect costs after 2 months (Table 4; Figure 2). After 4 months of treatment, the *cost reduction would increase to €138 million considering the cost/mg and to €213 million considering the cost/vial of drug.*

### 4.3 | Sensitivity analysis results for RM-HNSCC patients

Figure 3 illustrates the variables with the highest impact on the model results. One-way sensitivity analysis showed as

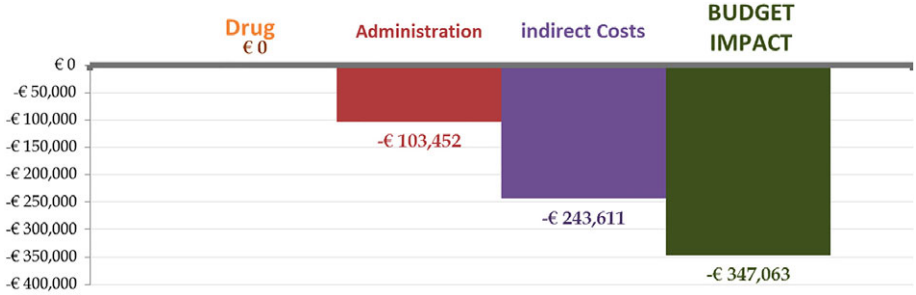


**FIGURE 1** Budget impact results, base-case vs EOW 50% scenario, per cost item (€). RM HNSCC, recurrent and/or metastatic head and neck squamous cell cancer; EOW, every other week [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 4** Budget impact results, base case vs EOW 100% scenario, 2 months

| Cost items | Expense | | |
|---|---|---|---|
| | **Base case (€)** | **EOW 100% scenario (€)** | **Budget impact (€)** |
| Drug cost (calculation/mg) | € 2 990 322 | € 2 990 322 | € 0 |
| Management cost/administration | € 413 808 | € 206 904 | −€ 206 904 |
| Indirect costs | € 974 445 | € 487 222 | −€ 487 222 |
| Total expense | € 4 378 574 | € 3 684 448 | −€ 694 126 |
| | 1 week | EOW 100% scenario | Tot. No. of treated patients |
| Base case treated patients | 609 | 0 | 609 |
| 100% treated patients scenario | 0 | 609 | 609 |

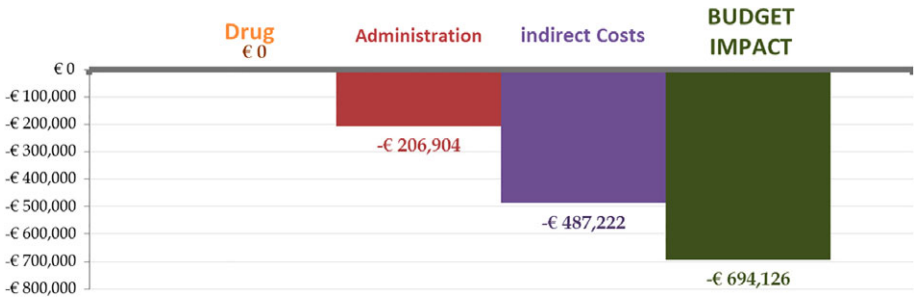


**FIGURE 2** Budget impact results, base-case vs EOW 100% scenario, per cost item (€). RM HNSCC, recurrent and/or metastatic head and neck squamous cell cancer; EOW, every other week [Color figure can be viewed at wileyonlinelibrary.com]

the model was most sensitive to the number of working days lost by patient or caregivers and when the drug cost was per vial instead of milligram. (Figure 3).

## 5 | DISCUSSION

In this analysis, we focused on the economic benefit of an EOW administration of Cetuximab vs a weekly schedule, as maintenance therapy.

Patients with RM-HNSCC not amenable to surgical salvage or radiation therapy may receive a combination of platinum-based chemotherapy and Cetuximab for a maximum of 6 cycles, followed by maintenance Cetuximab in case of clinical benefit and good tolerability. The weekly schedule of Cetuximab was used in the pivotal Extreme trial and thereby adopted in the clinical practice.

As confirmed by the PK data, the EOW 500 mg/m$^2$ schedule was similar in terms of exposure to the 250 mg/m$^2$ weekly dose; clinical data have confirmed the feasibility and

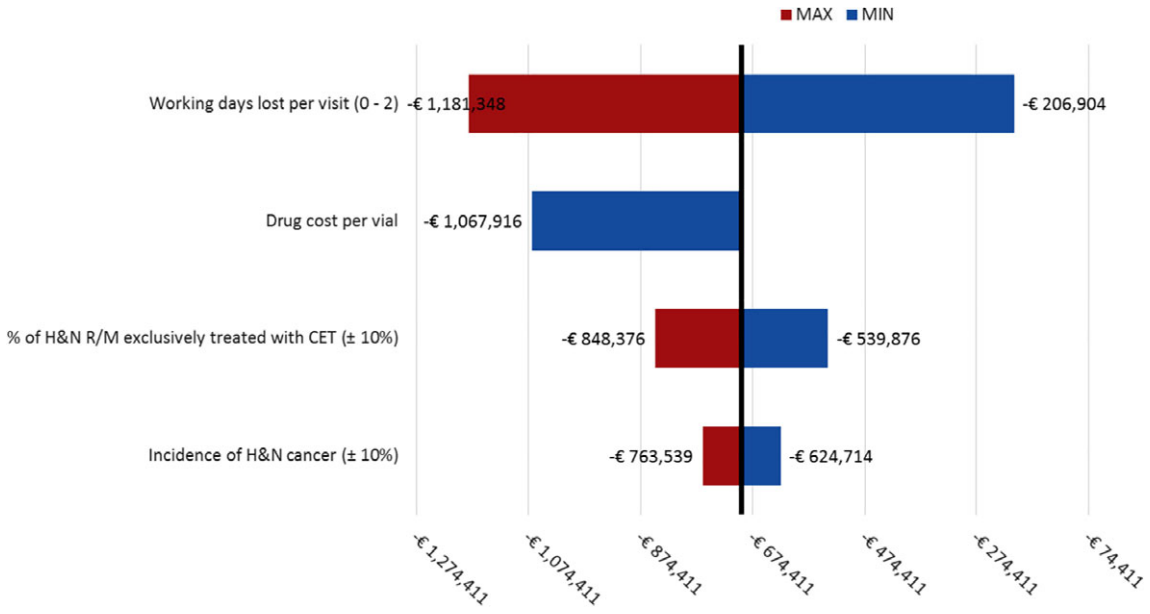


**FIGURE 3** One-way sensitivity analysis—case base budget impact vs EOW 100% scenario. H&N, head and neck; RM HNSCC, recurrent and/or metastatic head and neck squamous cell cancer; EOW, every-other week [Color figure can be viewed at wileyonlinelibrary.com]

activity of this approach, so justifying its broader use. The possible benefits of an EOW schedule in the maintenance phase rely on a better compliance of the patients, subject to a high number of cycles in the previous months; moreover, this advantage could reflect also into a benefit in the quality of life of the patients, receiving endovenous administration phased in longer time.

In our analysis, we showed that this simplified schedule could also reduce the costs of treatments both for the health system (direct costs) and for the society (indirect costs). The latter accounted for the major part of the potential savings following the adoption of an EOW administration of Cetuximab in Italy. This result was obtained assuming that after chemotherapy and Cetuximab, patients would benefit from an improvement of symptoms in the maintenance phase that would allow to gradually resume working.

Therefore, considering the preclinical and clinical premises and the economic benefits, we would suggest that the EOW schedule should be adopted as possible schedule of administration of Cetuximab in the maintenance phase, assuming that the disease remains controlled and the AEs are well tolerated.

Some limitations have to be underlined in our analysis. First, the epidemiological parameters were based on the data published in national reports, therefore with reference to the considered diseases; the number of treated patients with Cetuximab in Italy could be either overestimated or underestimated. However, in sensitivity analyses, these variables have been changed in a representative range of the national reality, allowing interval estimates able to represent a minimum and maximum impact of plausible expense.

Second, the model may have underestimated the real cost of patients treated with RM-HNSCC as it took into account a limited number of cost items. In particular, the model considered only the cost of Cetuximab and its administration and indirect costs deriving from patient or caregiver's absence from work. Transportation costs were not included due to the absence of a specific transportation program dedicated to chemotherapy administration patients funded by NHS. Also the costs due to AEs and/or disease progression and presenteeism or absenteeism for AEs were not included. However, in this case, we assumed that they would be identical between the two comparisons as confirmed by the therapeutic equivalence both in terms of safety and efficacy of the two administration methods of Cetuximab and hence not affecting the economic estimation. Finally, we did not include other possible economic saving in the EOW schedule, such as the possibility to reduce the drug waste in case of the use of the drug contained in vial of fixed dosage, which cannot be completely finished.

Finally, a third limitation is the lack of information on the lost working days in the two groups of treatment. The model conservatively assumed that the patients or caregivers lost at least one working day. However data may be underestimated due to the risk of AEs causing absence or reduced productivity or even a permanent exit from the labor market. In addition, caregivers could be also involved for an extra day after the day of the treatment.

In conclusion, the model represents a first attempt to quantify the economic impact of a change in treatment schedules of Cetuximab in Italy. Following the clinical rationale for its adoption, the analysis assessed the potential impact of an EOW administration from a societal perspective in which indirect costs resulted as the main driver. However, the new treatment strategy would also free resources in terms of lower hospital admissions that may be efficiently reallocated to maximize the work/hours of hospital staff and therefore have a positive impact from the hospital perspective.

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