Valorisation
In addition to the scientific value of this thesis presented in Chapters 2-6, the results of the research have also economic and societal value. In this chapter we put the results into a broader perspective and highlight its potential for policymakers and clinicians.

In the Netherlands, the annual incidence of invasive breast cancer is approximately 14,000 patients and for women between 30 and 50 years of age it’s number one cause of death. During the past decade the mortality has clearly decreased.\(^1\) The additional systemic treatment options, i.e., chemotherapy, HER2 targeted therapy and endocrine therapy, explain to a large extend the reduced risk of distant metastasis in more recent years. At least 40% of the patients diagnosed with invasive breast cancer are expected to be offered (neo-) adjuvant chemotherapy, nowadays consisting of a combination of cyclophosphamide, anthracyclines and taxanes.\(^2\) However, this combination is associated with an increased risk of FN, which can sometimes cause life-threatening infections. G-CSF prophylaxis reduces this risk, but comes with considerable costs. Approximately 50% of early breast cancer patients treated with (neo-) adjuvant chemotherapy are assumed to have an indication for G-CSF prophylaxis. In case of use of TAC chemotherapy, G-CSF prophylaxis is administered during all six chemotherapy cycles. However, as we noticed that FN incidence is the highest in the first two chemotherapy cycles, we hypothesized that to improve the cost-effectiveness of primary G-CSF prophylaxis, G-CSF use may be limited to the first two chemotherapy cycles opposed to the current practice of continued G-CSF prophylaxis. Therefore, we performed a randomized trial in which breast cancer patients were treated with chemotherapy with a more than 20% risk for FN with primary G-CSF prophylaxis during the first two chemotherapy cycles only (G-CSF 1-2) or to primary G-CSF prophylaxis throughout all chemotherapy cycles (G-CSF 1-6). Main clinical results showed that the incidence of FN was 10% in the G-CSF 1-6 cycles arm versus 36% in the G-CSF 1-2 cycles arm, with a peak incidence of 24% in cycle three, the first cycle without G-CSF prophylaxis. However, in the accompanying cost-effectiveness analysis, we demonstrated a major cost reduction of €3,500 per patient, if G-CSF prophylaxis is limited to the first two chemotherapy cycles. When extrapolated to the 2,800 breast cancer patients treated with prophylactic G-CSF during (neo-)adjuvant chemotherapy in the Netherlands, this would result in a yearly cost-saving of €9.8 million per year. Moreover, we must take into account the increasing incidence of breast cancer which negatively affects the total cancer care costs further.

However, the development of an FN event affects patients’ Health-related Quality of Life (QoL). FN disrupts normal life activities such as employment and childcare, and thus has financial and social implications for patients and their families. By reducing
the FN incidence with G-CSF prophylaxis subsequently QoL improves. Although we did not include the costs due to productivity loss, as most patients stop working during chemotherapy (equal for both treatment arms), the financial consequences if those aspects would have been considered lower the incremental outcome based on the different FN incidence.

In addition, in the Netherlands the willingness to pay (WTP) threshold of €80,000 per quality-adjusted life-years (QALY) is accepted. But, no survival benefit was shown from G-CSF prophylaxis in breast cancer patients. Hence, the dilemma is that from a cost viewpoint primary G-CSF prophylaxis will never be cost-effective, but from a clinical and societal viewpoint the question remains open whether we are willing to pay the loss in health benefit and whether we are willing to accept a small rate of neutropenic deaths that might otherwise have been prevented.

Very recently, new data came available showing the efficacy of sequential chemotherapy schedules that are associated with a lower risk of FN, thereby obviating the need of primary G-CSF prophylaxis in most patients. Only in patients treated with sequential AC-docetaxel above 60 years of age we would now recommend the use of G-CSF prophylaxis during the four docetaxel cycles. This implies a major cost reduction as we estimate that the use of G-CSF prophylaxis will be reduced by more than 50%.

In conclusion, this thesis has an economical as well as societal impact. It offers more information about different G-CSF prophylaxis and chemotherapy regimens for early breast cancer patients and its effect on bone marrow function and FN episodes. Whether we are willing to pay the loss in health benefit remains a societal discussion.
References

1. http://www.cijfersoverkanker.nl