Cost-utility analysis of recombinant human epidermal growth factor versus negative pressure therapy in the treatment of complicated diabetic foot ulcers in the Colombian setting


Authors
Diana Isabel Osorio Cuevas and Yamile Júbiz Pacheco

The objective of this study is to determine whether intra- and perilesional recombinant human epidermal growth factor is a cost-effective technology for the management of patients diagnosed with type 2 diabetes and a complicated diabetic foot ulcer without infection. A cost–utility analysis was made from the perspective of the Colombian health system, comparing intra- and perilesional recombinant human epidermal growth factor and negative pressure therapy. The health outcome used was quality-adjusted life years. A Markov model was designed. For the base case, a 5-year time horizon and weekly cycles were adopted. Transition probabilities were obtained from a systematic literature review. The identification and measurement of resources was based on clinical practice guidelines and expert consultation. The cost of drugs, procedures and supplies was obtained from official health information sources. In the base case scenario, negative pressure therapy is an intervention-dominated strategy for the outcome of quality-adjusted life years. It was concluded that the use of growth factor is a feasible option for the management of Wagner grade 3 or 4 diabetic foot ulcers due to the higher effectiveness and lower cost compared to negative pressure therapy.

Diana Isabel Osorio Cuevas *is Consultant, Edu-Essence SAS, Bogota, Colombia;* ***Yamile Júbiz Pacheco*** *is Head of the Diabetic Foot and Complex Wounds Unit, Colombian Diabetes Association, Bogota, Colombia.*

Diabetes is a disease that impacts high numbers of people worldwide. In Colombia in 2018, there were 1,305,492 prevalent cases of diabetes and 112,938 incident cases (Fondo Colombiano de Enfermedades de Alto Costo, 2019). Among people with diabetes, diabetic foot ulcers (DFUs) are a frequent and serious complication. It is estimated that the risk of developing a DFU ranges between 15% and 34%, affecting the quality of life of patients and impacting mortality (Armstrong et al, 2017; Ertugrul et al, 2017).

Diabetic foot is defined as the presence of infection, ulceration and/or deep tissue destruction associated with neurological abnormalities and various degrees of peripheral arterial disease in the lower limb of a person with diabetes. Loss of protective sensation due to neuropathy is present in up to 65% of people with diabetes, but associated with trauma is the major contributor to diabetic foot ulceration, almost 90% (Eleftheriadou et al, 2019).

DFUs have a major economic impact on patients, their families and society (Boulton et al, 2005). Therefore, the diabetic foot is a major public health problem (Edmonds et al, 2021). Foot complications in diabetes are a major cause of disability burden (Lazzarini et al, 2018). The recommended treatment for diabetic foot complications should be multidisciplinary, since care includes different factors, such as glycaemic control, revascularisation, surgical interventions and healing, among others (Eneroth and van Houtum, 2008; Edmonds and Foster, 2014). The goal of DFU treatment should be to rapidly and completely promote complete closure of the lesion to minimise the risk of complications and restore the patient's health-related quality of life to a pre-ulcer condition (Frykberg, 2002).

DFUs are associated with increased hospitalisations and lower extremity amputations in patients with this indication. In Colombia, there was a need for guidance for managing DFUs. To address this, the first clinical practice guideline (CPG) for the diagnosis and treatment of patients with complicated diabetic foot was published in 2019. The purpose of this document is to provide recommendations based on clinical evidence for the correct management of this complication and thus reduce the negative impact on the health and quality of life of patients (ACD, 2019).

The CPG recommendations include non-pharmacological interventions for the treatment of complicated DFUs. It has two recommendations on the use of negative pressure therapy (NPT), one as part of post-surgical management (debridement or amputation), with low quality of evidence; and one as part of the treatment of patients without surgical management, with very low quality of evidence (indicating that this alternative should be used when other management options fail).

In the pharmacological interventions, the CPG recommends treatment with recombinant human epidermal growth factor (rhEGF) for intra- and perilesional administration, with the purpose of reducing healing time (ACD, 2019).

NPT is used for the treatment of different types of wounds, including DFUs. Unfortunately in our environment, the usual clinical practice of application of this therapy is higher than the recommendations from clinical studies, protocols and guidelines. This treatment is recommended in the CPG when surgical management is not performed and when other alternatives do not achieve at least 50% of wound closure after 4 weeks of treatment (ACD, 2019).

NPT consists of the application of sub atmospheric pressure to the wound bed, as a form of topical and non-invasive treatment of the wound, facilitating healing through a multimodal action (National Institute for Health and Care Excellence, 2015). It has three main components: sponge (with or without silver) cut to the size of the wound, plastic material to obtain a hermetic seal, and the vacuum system, at a continuous suction of 75–125 mmHg for all types of wounds, applied every 3–5 days (Norman et al, 2020). The maximum treatment duration is between 20 and 32 days (Najarro Cid et al, 2014).

Intra- and perilesional administration of rhEGF is used in the treatment of complex wounds, including DFUs. The mechanism of action of rhEGF involves:

1. Rescue of stunted cells, generally fibroblasts.
2. Induction of proliferation of fibroblasts, myofibroblasts and vascular precursors (NOVO angiogenesis).
3. Cell migration.
4. Activation of genes for the synthesis of extracellular matrix.
5. Acceleration of the synthesis of alpha SMA by myofibroblasts.

The EGF exerts its action by binding to a specific receptor located on the membrane of the target cells – a glycoprotein with tyrosine kinase activity (Hermangus et al, 2015).

Although studies have evaluated the effectiveness and safety of these treatments for DFU, it is interesting to know the cost–utility benefit of these treatments in order to adequately guide decision-making on the most appropriate alternative.

The aim of this evaluation is to determine whether intra- and perilesional rhEFG is a cost-effective technology for the management of patients diagnosed with type 2 diabetes with complicated DFU without infection. The methodology employed is provided, framing the economic evaluation in a specific health setting, describing the analytical decision model and the information on the effectiveness and safety of the technology and the related costs. Subsequently, the results and their interpretation are provided, as well as the sensitivity analyses performed.

Methods

A cost–utility analysis was performed from the perspective of the health system, which corresponds to all direct medical costs associated with the use of the technologies and health benefits. The target population was patients over 18 years with a diagnosis of type 2 diabetes with a complicated DFU without infection.

Treatment consists of offloading, infection control, ischaemia control, wound debridement and adequate healing; however, adjuvant therapies are highly recommended to reduce closure time and ensure greater success in treatment, these include the use of rhEGF and NPT, which are recommended in the Colombian CPG (ACD, 2019). For this reason, the authors decided to compare rhEGF and NPT.

In addition to the two therapies compared, clinical evidence has provided results in favour

Table 1. Probabilities and distributions.					
Model parameters	Expected value	Sensitivity analysis parameters		Distribution	Source
		n	N		
Complete closure probability rhEGF[1] 75 µg	0.1436	54	365	Beta	(14,16)
Complete closure probability NPT[2]	0.0391	116	504		(17)
Incomplete closure probability rhEGF 75 µg	0.8564	22	365	Beta	(14.16)
Incomplete closure probability NPT	0.9609	130	504	Beta	(17)
Amputation probability rhEGF 75 µg	0.0185	15	365	Beta	(14,16)
Amputation probability NPT	0.0023	9	504	Beta	(17)
Death due to disease (all technologies)	0.0002	199	40,335	Beta	(19,20)
Death due to amputation (all technologies)	0.0017	9	185	Beta	(19,20)

[1]rhEGF: intra- and perilesional recombinant human epidermal growth factor [2]NPT: negative pressure therapy

of the use of dermal substitutes as one of the advanced alternatives in the treatment of DFUs. Therapy with dermal substitutes can be performed once conservative treatment does not improve more than 40% after the fourth week of treatment with other conventional therapies (Buendía Pérez et al, 2011).

In order to evaluate the possibility of including dermal substitute therapy as a comparator, we reviewed the available evidence by performing a rapid literature review. Some of the studies identified show positive results for patients with DFU (Wagner grade 1 or 2), venous ulcers and pressure ulcers. Some randomised clinical trials have reported adverse events, including infection requiring treatment with antibiotics, evolution to osteomyelitis (where the treatment of choice was intravenous antibiotics and surgical debridement), urinary and respiratory tract infections, and Charcot foot, but in such cases, none of the adverse events were attributed to the treatment (Buendía Pérez et al, 2011).

Dermal substitutes do offer some therapeutic advantages for the management of this type of patients and their relevance should be evaluated in the context of the evidence. However, taking into account the research question of the economic evaluation, the findings in terms of population and outcomes were not completely compatible with the main objective and, therefore, it was not considered pertinent to include them as a comparator in the study.

Within the search for evidence for the economic evaluation, no studies of any kind were found, including a comparison between rhEGF treatment and NPT for the treatment of DFUs, therefore, we used studies that served for indirect comparisons.

The time horizon for this evaluation corresponds to 5 years and weekly cycles; adjustments were made for a 5% discount rate on costs and benefits. The number of amputations avoided and Quality-Adjusted Life Years (QALY) were used as health outcomes.

To identify the costs and benefits of each alternative, a Markov model was designed that reflects the main health conditions within which a patient with the health condition of interest can move. This type of model allows the main therapeutic effects of the two alternatives to be evaluated: rhEGF and NPT. It was used to answer the economic research question and was the product of an update of an economic evaluation, fast literature review, discussion and refinement with subject-matter and methodological experts.

The model is composed of five mutually exclusive health conditions. These describe the possible transitions of a patient with a complicated DFU and without infection. The cycles of the model were weekly, taking into account clinical studies on the effectiveness of the two therapeutic alternatives once treatment is initiated.

Some assumptions were used in the proposed model:

- All patients enter the model in the health condition "Patients with ulcer".
- It is possible to remain in each cycle (lasting 1 week) in all health conditions except "Death".
- There was no transition between the health condition "Complete ulcer closure" and "Amputation". According to the subject-matter experts, this is a rare event within the population with this health condition.
- "Complex ulcer" comprises ulcers that have been present for a short time, but that are deep and expose vital structures; as well as persistent and recurrent ulcers.

The model parameters were taken from the primary studies included in the fast literature review, which specifically contained the

Table 2. Utility weightings.

Utility weightings	Expected value	Sensitivity analysis		Source
		Minimum	Maximum	
Patients with DFU	0.615	0.578	0.652	(20,21)
Complex ulcer	0.615	0.578	0.652	
Complete ulcer closure	0.68	0.62	0.72	
Amputation	0.505	0.396	0.615	

Table 3. Identification, measurement of resources (medications).

Medications						
Name	Strength	CUM[1]	Percentage of use	Dosage		Total presentation
				Weekly dose	Annual amount	
rhEGF	75 mcg of lyophilized powder	20022626	100%	225 mcg	1.800 mcg	75 mcg

[1]*CUM: Unique Medication Code* [2]*rhEGF: intra- and perilesional human recombinant epidermal growth factor.*

comparisons of interest for this evaluation. Subsequently, studies that made direct comparisons of interest to answer the evaluation question were identified. Finally, effectiveness and safety data extraction was performed in evidence tables. In total, five clinical trials were identified for both technologies with information for the calculation of the model health conditions; the population that participated in these studies had similar baseline characteristics, as did the comparators and outcomes *[Table 1]*.

A search was performed in PubMed, Google Scholar and the CEA Registry of Tufts University in order to identify the utility weights associated with each health condition of the proposed Markov model.

The effectiveness used in the model was taken from randomised clinical studies identified through a rapid review of effectiveness and safety literature provided in the first part of this paper *[Table 2]*. In this search, no studies were identified in which the health-related quality of life (HRQoL) of patients who received adjuvant treatment for DFU was reported, but two studies were identified in which the quality of life of people with diabetes was evaluated (Redekop et al, 2004). This study reported the differences in the quality of life when the patient had a DFU or lower limb amputation, so the utilities reported in this study were included.

Regarding the costs of each comparison alternative and of each health condition in the proposed model, identification, measurement and assessment of the resources was undertaken. A review of CPGs, care protocols, economic evaluations and consultations with subject-matter experts was carried out in order to structure a standard case for each scenario analysed. The costs that represent a significant impact on the results and that are differential between the comparison alternatives were considered.

Finally, the prices previously referenced in other studies were updated, using the 2019 Consumer Price Index in order to take into account the general price level and how this impacts the final prices of health resources.

The active ingredients of the drugs under analysis were consulted in the communications of the National Commission for Drug and Medical Device Prices, the agency in charge of regulating drug prices in Colombia, to verify whether the maximum sales prices of the technologies evaluated are currently regulated.

Subsequently, the database on drug prices in Colombia (SISMED) for 2019 was consulted, taking as a basis the sales price, the laboratory entity and the institutional channel. The average, minimum and maximum price per vial corresponds to the weighted price. Finally, the market share of the different drug presentations was calculated according to the number of units sold in the reported period (January–December 2019). The dose of the intervention technology was extracted from the drug's technical data sheet *[Tables 3 & 4]*.

Costs associated with each health condition were obtained from the model. The prices of the procedures are especially relevant for the care of patients who have complications at the time of ulcer closure, rehabilitations and amputation care. In the case of the first three health events, the values were taken from the Social Security Institute 2001 Rates Manual, one of the reference documents used in Colombia as a price reference for medical procedures, with an average adjustment of 30%, and considering a minimum adjustment of 25% and a maximum of 48%. For the estimation of amputations,

Table 4. Resource assessment (medications) (dollars).										
	Medications									
Name	Minimum vial value[2]	Average vial value	Maximum vial value[3]	VMR[1]	Minimum dose value[2]	Average dose value[3]	Maximum dose value	Minimum annual value	Average annual value	Maximum annual value
rhEGF[4]	443.39	447.76	539.04	539.04	1,330.18	1,343.27	1,617.12	10,641.44	10,746.18	12,936.98

[1]VMR: Maximum recovery value [2]Resolution 3514 issued on December 26, 2019 [3]SISMED 2019 [4]rhEGF: intra- and perilesional recombinant human epidermal growth factor

Table 5. Comparator technology cost.

Name	CUPS[1] (If applicable)	Total quantity (per week)	Percentage of use	Average value (dollars)	Total value (dollars)
Debridement with subatmospheric pressure device placement (negative pressure therapy)	862601	2	100%	679.87	1,359.74

[1]CUPS: Unique classification of health procedures. Resolution 3495 of 2019

Table 6. Cost of health status rhEGF[1].

Health condition	Total cost (dollars)	Description
Patient with diabetic foot ulcer	1,343.27	rhEGF treatment (3 vials per week)
Complex ulcer	1,349.71	rhEGF treatment + ulcer rehabilitation
Complete ulcer closure	1,929.19	rhEGF treatment + rhEGF health care (Romero et al.)
Amputation	1,138.91	Amputation + post-amputation rehabilitation

[1]hEGF: intra- and perilesional recombinant human epidermal growth factor

the SOAT Rates Manual, a document for drug prices used for negotiation and definition of rates between service providers and insurers, was used.

For estimating the cost of the procedure established as a comparative technology for the economic evaluation, a direct consultation was made with the Health Promoting Entities, health insurance companies in Colombia. This process was carried out taking into account the lack of timely access to the UPC (Capitation Payment Unit) sufficiency database administered by the Ministry of Health and Social Protection. The sales price to a particular patient was taken into account, given that prices may vary depending on the negotiation agreements between insurers and health service providers *[Table 5]*.

Finally, the associated costs were obtained for each of the health conditions of the Markov model. The data used in the estimation of health care costs for an amputation were obtained from the CPG for the diagnosis and preoperative, intraoperative and postoperative treatment of the amputee, the prescription of the prosthesis and comprehensive rehabilitation published by the Ministry of Health and Social Protection in 2015 (Ministerio de Salud y Protección Social, 2015). The resources included are hospitalisation, surgical procedure, prophylactic antibiotic and rehabilitation during hospitalisation. In addition, the cost of post-amputation rehabilitation is included. The values were updated with the Consumer Price Index for the year 2019.

The cost of complex ulcers includes the treatment and healthcare received by the average patient, including healing and grafting. The latter is the most frequent method of treating these types of ulcer *[Tables 6&7]*.

Results

Table 8 and *Figure 1* show the results of the base case, ordering the alternatives from lowest to highest cost. NPT is the most expensive alternative at $US213,330, followed by rhEGF with a cost of $US67,822. The therapeutic alternative of rhEGF is a dominant strategy; its average cost is lower compared to the NPT alternative. Likewise, it contributes more QALYs for these patients (2.64 versus 2.39). This indicates that an additional QALY has a better cost-effectiveness ratio in the case of growth factor.

Once the distributions for each of the variables of analysis, health outcomes and cost, have been selected, a probabilistic sensitivity analysis is performed in order to evaluate the uncertainty as a whole.

This analysis allows us to know the probability that each technology has to be cost-effective taking into account an availability-to-pay threshold of one or three times the country's per capita GDP; for 2019 this was $US6,238.07 and $US18,714.21, respectively. *Figure 2* allows us to observe that given that the rhEGF alternative is a dominant strategy, the probability of being cost-effective is high at different values of the

Table 7. Cost of health condition NPT[1].		
Health condition	**Total cost (dollars)**	**Description**
Patient with diabetic foot ulcer	1,359.74	NPT treatment (2 times per week)
Complex ulcer	1,366.18	NPT treatment + ulcer rehabilitation
Complete ulcer closure	1,945.66	NPT treatment + NPT health care (Romero et al.)
Amputation	1,138.91	Amputation + post-amputation rehabilitation

[1]NPT: negative pressure therapy

Table 8. Base case results (dollars).					
Alternatives	**Cost**	**Incremental cost**	**Effectiveness**	**Incremental effectiveness**	**ICER[4]**
AVAC[1]					
rhEGF[2]	67,822.03		2.64		
NPT[3]	213,330.91	145,508.88	2.39	(0.24)	DOMINATED

[1]1QALYs: quality-adjusted life years [2]rhEGF: intra- and perilesional recombinant human epidermal growth factor [3]NPT: negative pressure therapy [4]ICER: incremental cost-effectiveness ratio

Figure 1. Cost-effectiveness plane.

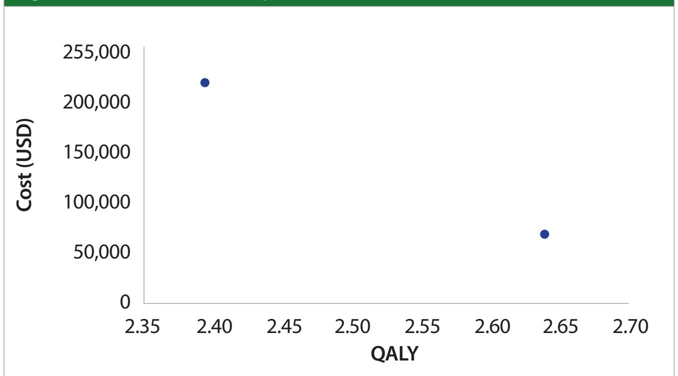
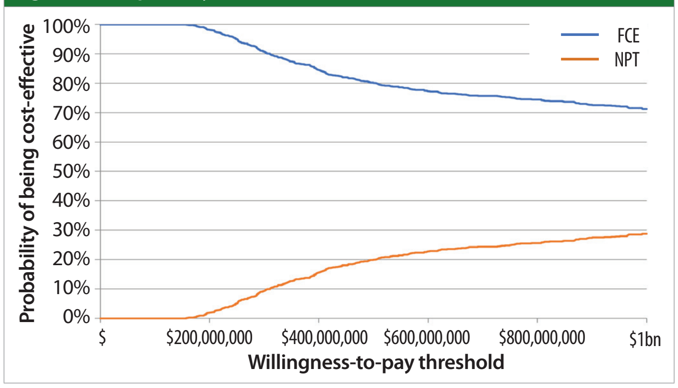


Figure 2. Acceptability curve.



threshold. This result shows a positive trend at values above 1 billion pesos, compared to the NPT alternative.

Discussion and conclusion

One of the advantages of rhEGF for intra- and perilesional use is the treatment time, since it is only applied for 8 weeks, by which time the effectiveness is seen in a large number of patients (Fernández-Montequín et al, 2009; Gómez-Villa et al, 2014) which, according to the literature, is given for 20 weeks on average (Eneroth and van Houtum, 2008).

One of the main limitations of the data lies in the fact that the characteristics of the studies do not allow the development of an indirect comparison between NPT and other therapeutic strategies versus rhEGF for intra- and perilesional use. Additionally, no head-to-head studies were identified between the other therapeutic options used in Colombia and the technology of interest in this evaluation.

As shown in the base case analysed, the use of rhEGF for intra- and perilesional use is a cost-effective option for the treatment of Wagner grade 3 and 4 ulcers. It is more effective and less expensive than the comparison alternative. According to the sensitivity analyses provided, the dominance of intra- and perilesional rhEGF in the face of variations in the availability-to-pay threshold is confirmed.

It is important to keep in mind is that the treatments, NPT and rhEGF are not competitors, but rather they are complementary therapies, which would increase the possibility of a more successful and fast result.

Finally, rhEGF for intra- and perilesional use is a good option to be taken into account in the inclusion of the Health Benefits Plan for its use in patients who present with Wagner grade 3 or 4 DFUs. WINT

References

Armstrong DG, Boulton AJM, Bus SA (2017) Diabetic foot ulcers and their recurrence. *N Engl J Med* 376(24): 2367–75

Asociación Colombiana de Diabetes (2019) *Clinical Practice Guideline for the Diagnosis and Treatment* *of Patients with Complicated Diabetic Foot*. Available at: https://asodiabetes.org/wp-content/uploads/2021/04/GuiaPractica-1.pdf (accessed 18.10.2021) [in Spanish]

Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J (2005) The global burden of diabetic foot disease. *Lancet* 366(9498): 1719–24

Buendía Pérez J, Vila Sobral A, Gómez Ruiz R et al (2011) Complex wound management with vacuum assisted therapy. Experience in the past 6 years at the University Clinic of Navarra, Pamplona (Spain). *Cir Plast Ibero-Latinoamericana* 37(Suppl 1): S65–71 [in Spanish]

Edmonds M, Manu C, Vas P (2021) The current burden of diabetic foot disease. *J Clin Orthop Trauma* 7:88–93

Edmonds ME, Foster AVM (2014) *Managing the Diabetic Foot.* 3rd edn. Chicester, West Sussex: John Wiley & Sons

Eleftheriadou L, Kokkinos A, Liatis S et al (2019) *Atlas of the Diabetic Foot*. 3rd edn. Chicester, West Sussex: John Wiley & Sons

Eneroth M, van Houtum WH (2008) The value of debridement and Vacuum-Assisted Closure (V.A.C.) Therapy in diabetic foot ulcers. *Diabetes Metab Res Rev* 24(Suppl 1): S76–80

Ertugrul BM, Lipsky BA, Guvenc U (2017) An assessment of intralesional epidermal growth factor for treating diabetic foot wounds the first experiences in Turkey. *J Am Podiatr Med Assoc* 107(1): 17–29

Fernández-Montequín JI, Valenzuela-Silva CM, Díaz OG, et al (2009) Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: Multicenter, randomised, placebo-controlled, double-blind study. *Int Wound J* 6(6): 432–43

Fondo Colombiano de Enfermedades de Alto Costo (2019) *Situación de la enfermedad renal crónica, hipertensión arterial y diabetes mellitus en Colombia.* Available at: https://bit.ly/3m0x1gd (accessed 12.12.2021)

Frykberg RG (2002) Diabetic foot ulcers: pathogenesis and management. *Am Fam Physician* 66(9): 1655–62

Gómez-Villa R, Aguilar-Rebolledo F, Lozano-Platonoff A et al (2014) Efficacy of intralesional recombinant human epidermal growth factor in diabetic foot ulcers in Mexican patients: A randomized double-blinded controlled trial. *Wound Repair Regen* 22(4): 497–503

Hermangus JF, Carlos R, Konschot L (2015) Use of negative pressure therapy in the treatment of complex wounds. 4 case reports *Asoc Médica ABC* 60(2): 141–7 [in Spanish]

Lazzarini PA, Pacella RE, Armstrong DG, Van Netten JJ (2018) Diabetes-related lower extremity complications are a leading cause of the global burden of disability. Diabet Med 35(9): 1297–9

Najarro Cid F, García Ruano Á, Luanco Gracia M et al (2014) Negative pressure therapy in the management of complex wounds in orthopedic surgery: innovation and indication. *Rev la Soc Andaluza Traumatol y Ortop* 31(2): 17–23 [in Spanish]

National Institute for Health and Care Excellence (2015) Diabetic foot problems: prevention and management. London: NICE. Available from: http://www.nice.org.uk/ng19 (accessed 18.10.2021)

Norman G, Goh EL, Dumville JC et al (2020) Negative pressure wound therapy for surgical wounds healing by primary closure. *Cochrane Database Syst Rev* 6(6): CD009261

Redekop WK, Stolk EA, Kok E et al (2004) Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. *Diabetes Metab* 30(6): 549–56