Appendix 1 (as supplied by the authors): Supplementary information

Methods

Model validation

The following validation techniques are based on ISPOR-SMDM recommended practices for model transparency and validation(1). As the prevention of DFUs is not well studied in literature(2), it is important to note that this model serves as a framework for future research in this area.

Face validity

Multiple steps were taken to ensure face validity. The problem formulation process determined a focus on a Canadian context, identified a population with diabetes who are low to high risk of DFUs, defined a TM intervention that aims to prevent DFUs, and selected a time horizon that reflects the natural history of DFUs.

The model structure was constructed and rigorously adjusted by experts in modelling (WI) and diabetic foot care (KC) to emulate recommended practices in DFU prevention according to the International Working Group for the Diabetic Foot. Since the modelling of DFU prevention is in its early stages in literature, data applicable to this model was limited. With this in mind, the data sources consulted for the construction of the model were verified for appropriate study design and applicability of results. Decisions were made to include certain DFU states and to exclude others, such as not distinguishing between minor and major amputations. Also, the complexity of DFU progression was not modelled, due lack of applicable data for this progression and that representing it as a number of discrete states is clinically impractical.

Verification

To ensure the correct mathematical equations were used in the model, a structured walk-through of the code was conducted by CB to WI. To ensure that the model performed according to its specification, extreme-value analysis was conducted by predicting the behaviour of the model when a certain parameter is adjusted.

Cross Validity

Since no other studies have explored the cost-effectiveness of TM, we identified other studies with models that evaluate the cost-effectiveness of DFU prevention.

The first study identified was by Tennvall and Apelqvist, 2001 where a cost-utility analysis was conducted to evaluate the prevention of DFUs and amputations(3). The prevention strategy defined was patient education, foot care, and footwear. It was found that DFU and amputation incidence needs to be reduced by 25% to be cost-effective, which was identified as ICER < €100,000/QALY. This is similar to the results our model produced as there is an increase in cost per QALY gained. However model structures are different. For example, the model did not include the stratification of risk groups, but instead the model was simulated individually for each group at risk for DFUs. Also, the healing rates of DFUs were assumed to be same, regardless of which risk group the DFU originated from. This assumption can influence the

results, as DFUs with and without peripheral arterial disease can heal at different rates(4). Similarly, Ortegon et al., 2004 also varied the effectiveness (between 10%-90%) of the interventions to identify thresholds of cost-effectiveness (5). Also, the model included states for risk groups before DFU development. However, the cohort was assumed to be all in the lowest risk group and transitioned into the others over time, which is not representative of a diabetic population. Similar to Tennvall and Apelqvist 2001, this model also assumed DFUs healed at the same rates regardless of risk group. As expected, the outcomes (ICERs) between this model and ours were different. However, both models showed that, depending on prevention effectiveness, there is an increase in cost per QALY gained. Lastly, Barshes et al. 2017, estimated cost-savings in diabetic foot ulcer prevention efforts(6). Specifically, this study explored the effects of improved prevention (primary) and treatment (secondary) by varying its effectiveness. A major distinction is that this model identifies annual prevention cost thresholds for cost-savings, rather than the traditional ICER. This makes it's difficult to compare outcomes of the models. In addition, the model did not include a cost for stratifying a person into a risk group, which can significantly change the results presented. However, similar methodologies were used in both models, such as varying effectiveness thresholds and incorporating the stratification of the cohort into risk groups in order to determine appropriate screening strategies. Also, this model used a one-month cycle length, which may not reflect how DFUs progress in current available research, as follow-up visits are 1 year on average.

Definitions of study parameters

Pre-DFU

The risk groups defined in this paper were based on the guidelines from *Best Practice Recommendations for the Prevention and Management of Diabetic Foot Ulcers* published by Wounds Canada (See Table 1). These recommendations were used to define 3 risk groups for our model: low risk, moderate risk, and high risk (recurrent DFU). The high-risk group assumed that recurrent DFUs either recurred at the same spot as the prior DFU, or in a new spot, as many studies do not distinguish between the types. The transition probability into the moderate risk group was derived from the estimate of 1/3 people with diabetes having peripheral artery disease (PAD) by the American Diabetes Association and Barshes et al. 2013. The mortality rate for the moderate risk group was based on a study by Mueller et al. 2014 that reported mortality rates in patients with diabetes and PAD. The mortality rate for the low risk group was based on Statistics Canada 2008 data on the number of deaths per 100,000 population with diabetes. Amputation rates prior to DFU formation was based on a study that observed lower limb amputation rates among diabetes patients without foot ulcer in Medicare and private insurance (12).

DFU

The transition probability from a low risk group to a moderate risk group was obtained from a previous cost-effectiveness study by Ortegon et al. 2004 (5). The transition probabilities for the development of low-risk and moderate-risk DFUs were derived from Lavery et al. 2008, where the incidence of DFUs were observed in people with diabetes stratified by risk factors with preference for conservative estimates (13). Amputation rates from low risk, moderate risk and

recurrent DFUs were compared between five studies to derive the probabilities used in this model (16-21) . Since little data exists on mortality rates for recurrent DFUs, and Orneholm et al. 2017 (17) reports a significantly lower mortality rate than rates reported for DFUs with PAD, it was assumed that the mortality rate is the same as having a moderate risk DFU.

Amputation

The amputation state was assumed to include both major and minor amputations and does not distinguish the cost difference between the two. The effects of this is further explored in the sensitivity analysis. When in the amputated state, a person can transition into either the healed amputation state or death. Mortality rates are adjusted as time increases via Markov tunnel states. As time increases, mortality rates increase. This increase is derived from Kaplan Meier survival estimates in Aulivola et al. 2004 and Fortington et al. 2013 (20, 21) (Figure 2).

Probability sensitivity analyses were achieved using Dirichlet and beta distributions for all state transition probabilities (22).

Cost and utilities values

Measurement and Valuation of Outcomes

Estimates of health utilities associated with each state was obtained from an extensive review of utility values in type 2 diabetes specific for economic modelling (23). This review did not include a utility value for healed DFUs, which was derived from Redekop, 2000 (24).

Resource Use and Costs

The costs of treatment were based on annual estimates of hospital costs from the Canadian Institute for Health Information's Patient Cost Estimator (25). This report included the cost of Diabetes with Foot Ulcer, Amputation of Hand/Foot, Biopsy of Bone and Orthopedic Aftercare (SI Table 3). Hopkins et al. 2015 reported that the average number of admissions per prevalent case was 0.66, so this was used to adjust the cost proportion in the DFU state (26).

The physician fees were based on the Schedule of Benefits: Physician Services under the Health Insurance Act (5) (SI Table 4). Validated by KC, billing codes descriptions used for DFUs are Wound and ulcer debridement and Wound and ulcer debridement extending into any of the following structures: tendon, ligament, bursa and/or bone. The average of these costs was used in this model. Physician fees for amputations are the average costs of Amputation-Bone Code-Musculoskeletal System for Metatarsal/phalanx disarticulation, Ray(single), Symes, Transmetatarsal/transtarsal, Terminal Symes, and the average costs of Biopsies for Need-Punch, Needle – under general anasethetic, Needle – open, and Joint – open. Physician fees for screening and prevention visits prior to a DFU (for both in-person and telemedicine) and follow-up visits with a healed DFU were based the average costs for Diabetic screening with a family physician, and endocrinologist visits. Table 3 lists all of the billing codes used to derive costs in the model.

The cost of a TM solution was derived from the operating costs of the Ontario Telemedicine Network (OTN) in a financial statement from 2016 (27). The services provided by the OTN leverages similar technology required for a hypothetical telemonitoring intervention for DFUs

and was used as our baseline cost. The cost of the TM device was derived from Fasterholdt et al. 2016 using www.xe.com, where a similar device was used to monitor DFUs (28). Since this cost is sourced from a different jurisdiction and represents a small portion of total costs, laborious cost conversion is irrelevant. The physician fees associated with the use of the device for screening was assumed to be the combined cost of telemedicine billing codes defined in the OHIP Billing Information for Telemedicine Services September 2011 and the cost of a regular in-person screening visit. This assumption was made as the type of interaction via the TM device is not defined within the Schedule of Benefits.

Appendix to: Boodoo C, Perry JA, Leung G, et al. Cost-effectiveness of telemonitoring screening for diabetic foot ulcer: a mathematical model. *CMAJ Open* 2018. DOI:10.9778/cmajo.20180088.

Tables and Figures

Supplementary Table A1. Risk groups for developing DFUs used in models based on International Working Group on the Diabetic Foot (IWGDF) guidelines reported by Wounds Canada.

Clinical state in model	**IWGDF**(7)	**Recommended Professional Follow-up(7)**	**Characteristics**
Low Risk for DFU	0	Every 12 months	No loss of protective sensation No peripheral arterial disease (PAD)
	1	Every 4-6 months	No loss of protective sensation ± non-changing foot deformity
Moderate Risk for DFU	2a&b	Every 3 months	PAD and/or deformity ± loss of protective sensation
DFU Recurrence	3a&b	Every 1-3 months	Presence of diabetes with previous history of ulceration/amputation
Active DFU states	Urgent	Immediate referral	Open ulcer ± infections Charcot foot

Appendix to: Boodoo C, Perry JA, Leung G, et al. Cost-effectiveness of telemonitoring screening for diabetic foot ulcer: a mathematical model. *CMAJ Open* 2018. DOI:10.9778/cmajo.20180088.

Supplementary Table A2. All transition probability parameter estimates, and sources used in Markov Model for current screening efforts in Canada. All telemonitoring Markov Models used same parameter estimates, except DFU incidence rates. Specifically, the transition from a healed DFU state to a recurrent DFU state was decreased by 5%-40% (high-risk) and the transition from a low risk, moderate risk and healed DFU state to a DFU state was decreased by 5%-40% (population-based).

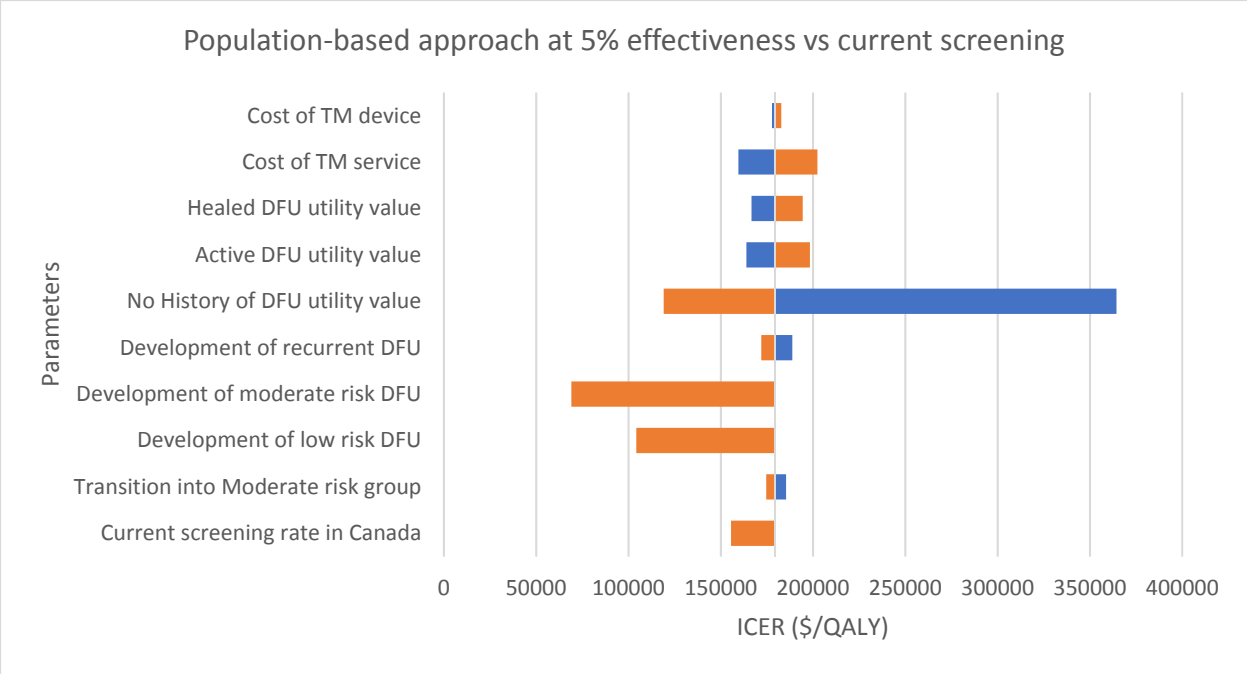
Transitions		*Value(Range)*	*Source*
Person with Diabetes	At low risk of DFU	66.83%	
	At moderate risk of DFU	33.0%	American Diabetes Association, 2014(8)
	Amputation	0.01%	Rice et al., 2014(12)
	Death	0.16%	Statistics Canada, 2014(11)
Amputation	Healed amputation	See figure 2	
	Death	See figure 2	Aulivola et al., 2004(20)
At low risk of DFU	At low risk of DFU	99.46%	
	Amputation	0.01% (0.00667 - 0.01334)	Rice et al., 2014(12)
	Develop low risk DFU	0.3% (0.18 - 0.41)	Lavery et al., 2008(13)
	Death	0.16%	Statistics Canada, 2014(11)
	At moderate risk of DFU	0.07%	Ortegon et al., 2004(5)
Develop low risk DFU	Develop low risk DFU	52.45%	
	Healed DFU	45.71%	Prompers et al., 2008(4)
	Amputation	0.67% (0.3 - 0.77)	Lavery et al., 2008(13), Moulik et al., 2003(8), Prompers et al., 2008(4)
	Death	1.17% (1.01 - 2.57)	Prompers et al., 2008(4), Morbach et al., 2012(16)
At moderate risk of DFU	At moderate risk of DFU	99.38%	

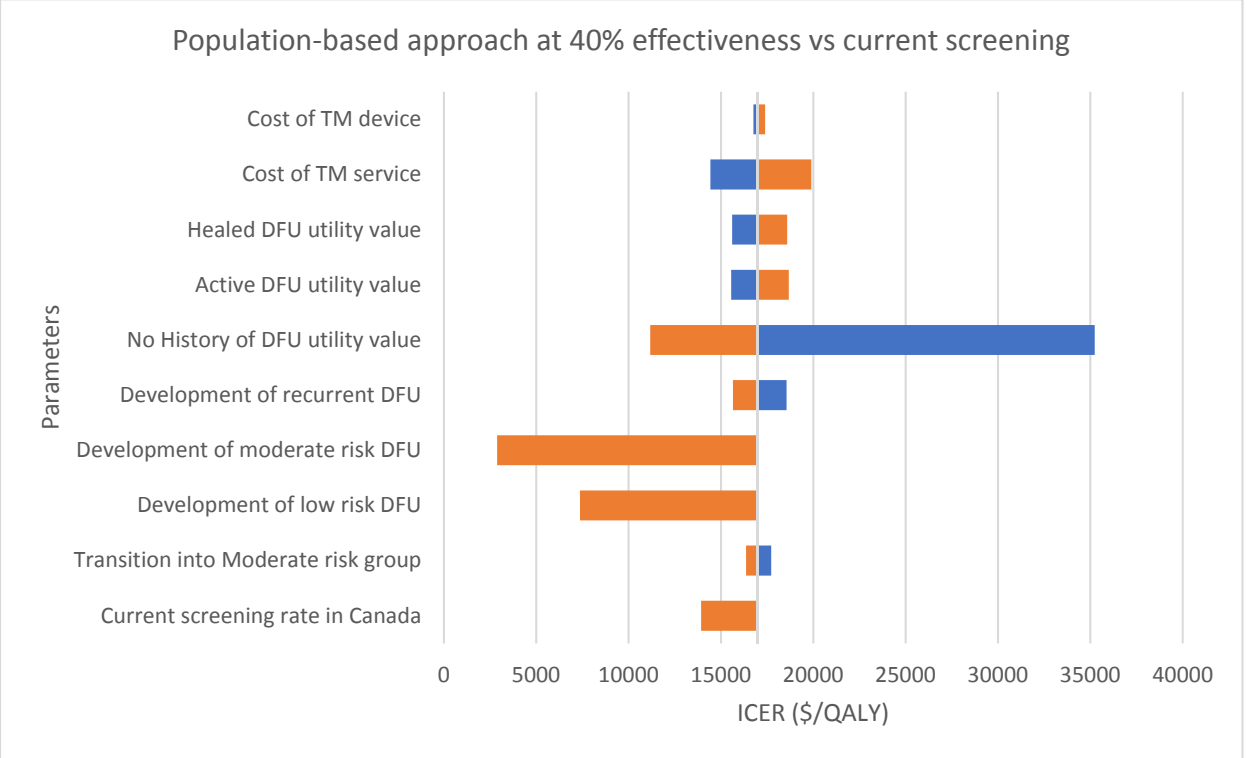
Appendix to: Boodoo C, Perry JA, Leung G, et al. Cost-effectiveness of telemonitoring screening for diabetic foot ulcer: a mathematical model. *CMAJ Open* 2018. DOI:10.9778/cmajo.20180088.

	Amputation	0.01%	Rice et al., 2014(12)
	Develop high risk DFU	0.45% (0.27 - 1.31)	Lavery et al., 2008(13)
	Death	0.67%	Mueller et al., 2014(10)
Develop moderate risk DFU	Develop high risk DFU	61.68%	
	Healed DFU	32.32%	Prompers et al., 2008(4)
	Amputation	2.74% (0.063 - 8.54)	Lavery et al., 2008(13), Morbach et al., 2012(16), Oyibo et al., 2001(15), Prompers et al., 2008(4)
	Death	3.26% (3.26 - 8.07)	Prompers et al., 2008(4), Morbach et al., 2012(16)
Healed DFU	Healed DFU	87.06%	
	Develop recurrent DFU	11.21% (7.17 - 15.66)	Armstrong et al., 2017(18), Dubsky et al., 2013(13)
	Amputation	0.01%	Rice et al., 2014(12)
	Death	1.01% (0.57 - 1.56)	Orneholm et al., 2017(17)
Recurrent DFU	Recurrent DFU	81.78%	
	Healed DFU	11.51%	Orneholm et al., 2017(17)
	Amputation	3.45% (0.68 - 3.45)	Lavery et al., 2008(5), Orneholm et al., 2017(17)
	Death	3.26%	Prompers et al., 2008(4), Morbach et al., 2012(9), Orneholm et al., 2017(17)

Supplementary Table A3. Canadian Institute for Health Information Patient Cost Estimator (25) data used for costing DFUs and amputations.

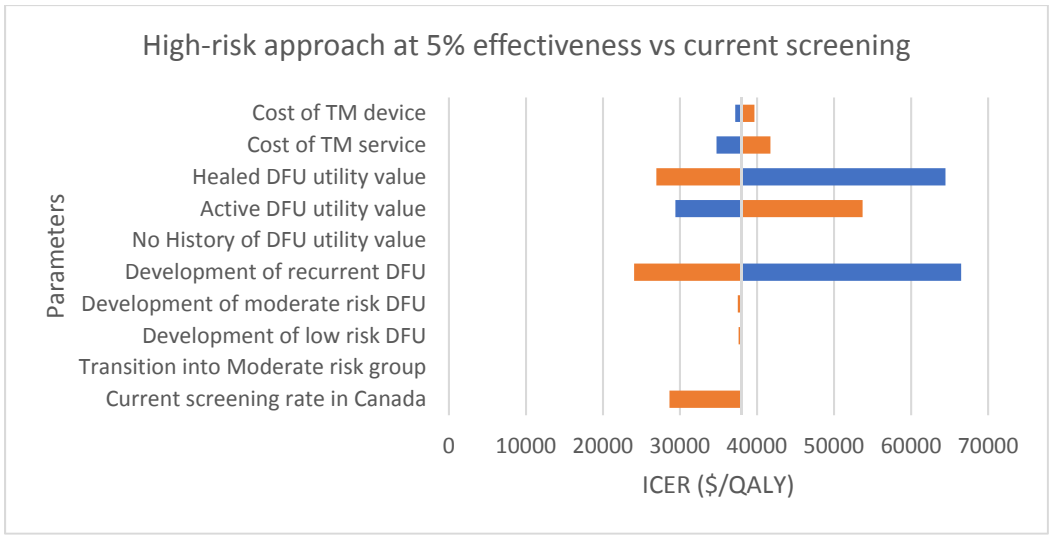
Case Mix Group	Age Group	Estimated Average Cost	Estimated Average Cost (all age groups)	Average Acute LOS days
402 Diabetes with Foot Ulcer	18-59 Years (Adult)	$ 9,984.36	$ 10,250.73	7.8377483
	60-79 Years (Adult)	$ 10,647.33	$ 10,250.73	9.4900459
	80+ Years (Adult)	$ 9,822.41	$ 10,250.73	9.8122271
183 Amputation of Hand/Foot	18-59 Years (Adult)	$ 9,864.15	$ 10,071.53	8.6962963
	60-79 Years (Adult)	$ 10,153.88	$ 10,071.53	9.4888889
	80+ Years (Adult)	$ 10,138.53	$ 10,071.53	12
342 Biopsy/Invasive Inspection of Bone	1-7 Years (Paediatric)	$ 5,406.19	$ 5,145.99	5.0833333
	8-17 Years (Paediatric)	$ 4,069.78	$ 5,145.99	1.8627451
	18-59 Years (Adult)	$ 4,758.34	$ 5,145.99	2.6986301
	60-79 Years (Adult)	$ 5,387.70	$ 5,145.99	3.6666667
	80+ Years (Adult)	$ 9,163.79	$ 5,145.99	12.434783

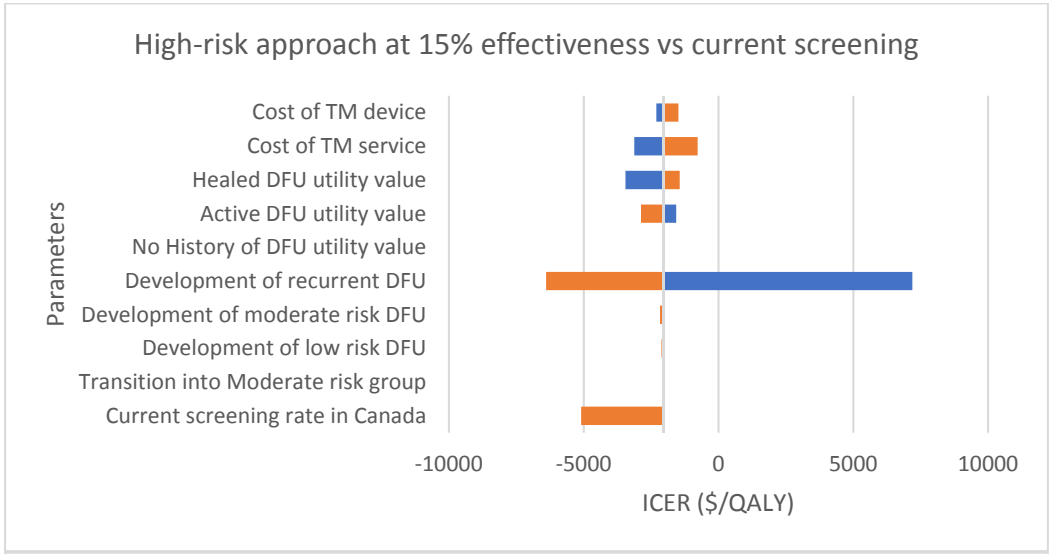


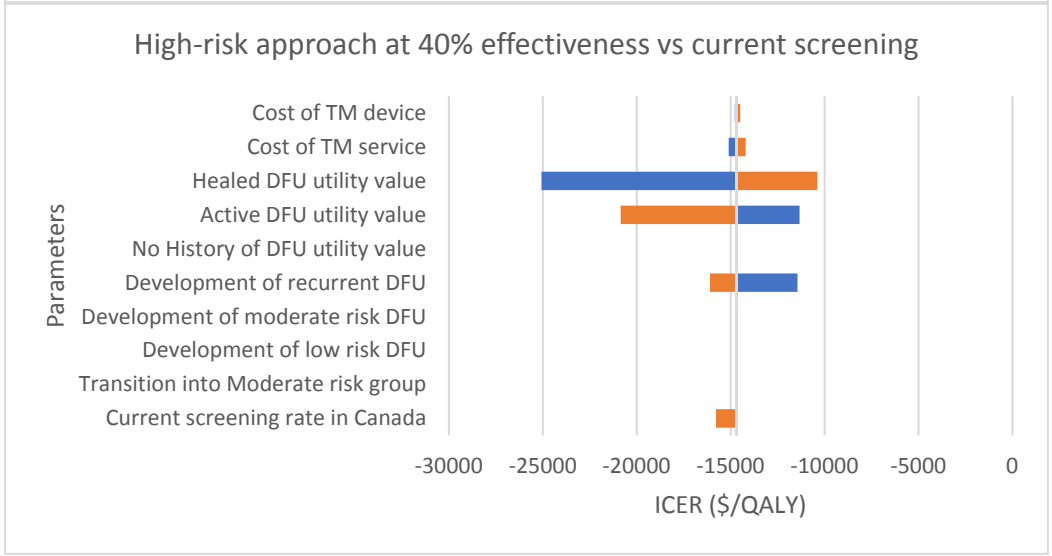


Supplementary Figure A1: Population-based approach one-way sensitivity analyses. Analyses were run for effectiveness values ranging from 5% to 40% in increments of 5%, but since trends changed very little only the highest and lowest effectiveness values are shown.

Appendix to: Boodoo C, Perry JA, Leung G, et al. Cost-effectiveness of telemonitoring screening for diabetic foot ulcer: a mathematical model. *CMAJ Open* 2018. DOI:10.9778/cmajo.20180088.

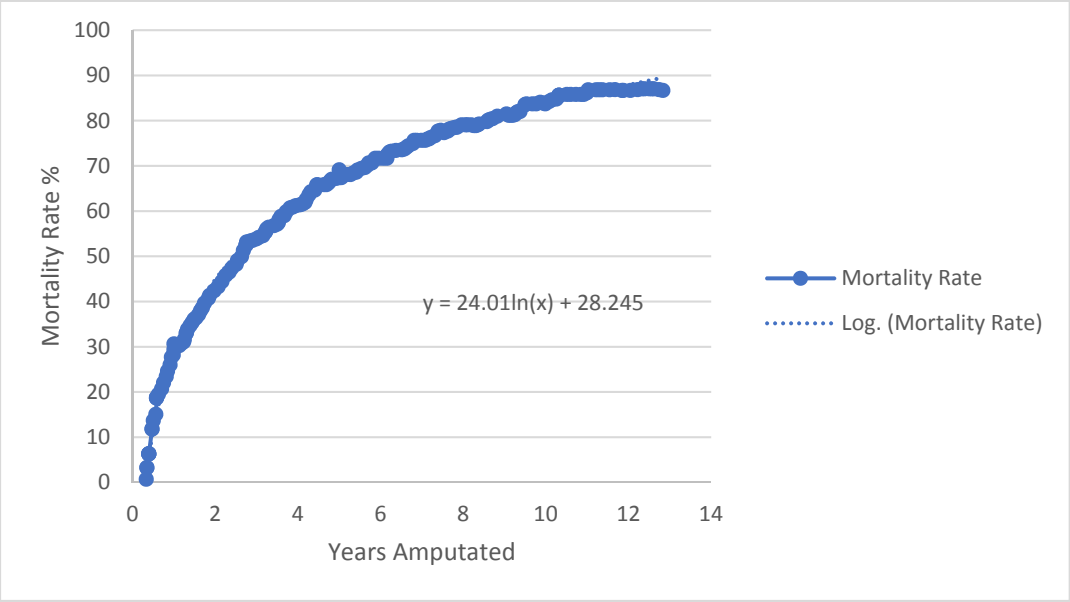






Appendix to: Boodoo C, Perry JA, Leung G, et al. Cost-effectiveness of telemonitoring screening for diabetic foot ulcer: a mathematical model. *CMAJ Open* 2018. DOI:10.9778/cmajo.20180088.

Supplementary Figure A2: High-risk approach one-way sensitivity analyses. Analyses were run from 5% effectiveness to 40% effectiveness in increments of 5%. Trends changed more dramatically than the population-based analysis, and representative tornado diagrams are shown.



Supplementary Figure A3: Kaplan Meier curve derived from Aulivola et al. 2004 (20) and Fortington et al. 2013 (21) mortality rates for diabetics with lower extremity amputations.

Appendix to: Boodoo C, Perry JA, Leung G, et al. Cost-effectiveness of telemonitoring screening for diabetic foot ulcer: a mathematical model. *CMAJ Open* 2018. DOI:10.9778/cmajo.20180088.

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