



Should Vitamin B12 Tablets be Included in More Drug Formularies? An Economic Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular Vitamin B12 for Alberta Seniors

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5 Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular Vitamin B₁₂ for
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8 Alberta Seniors
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ABSTRACT:

Objectives: The aim of this study is to estimate the cost-savings attainable if all patients aged ≥ 65 in Alberta and currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

Setting: Primary care setting in Alberta, Canada.

Participants: Seniors age 65 and older currently receiving intramuscular vitamin B₁₂ therapy.

Intervention: Oral vitamin B₁₂ therapy at 1000 mcg per day versus intramuscular therapy at 1000 mcg per month.

Primary and Secondary Outcome Measures: Cost-saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring, and physician visit fees.

Results: Over 5 years, if all Albertans age 65 and older who currently receive intramuscular B₁₂ are switched to oral therapy, our model found that CAD \$13,975,883 can be saved. Even if no additional physician visits are billed for among patients receiving IM therapy, \$8,444,346 could be saved from reduced administration costs alone.

Conclusions: Oral B₁₂ therapy has been shown to be an effective therapeutic option for patients with vitamin B₁₂ deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation.

To ensure judicious use of limited health resources, clinicians and formulary committees are encouraged to adopt oral B₁₂ therapy as a clinically- and cost-effective first line therapy for vitamin B₁₂ deficiency.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- Minimal assumptions built into the model, as exact costs and the exact number of eligible residents comprising the population were available
- Three randomized controlled trials and two prospective case series support our use of a cost-minimization analysis approach
- Comprehensive sensitivity analyses employed using Monte Carlo simulation to incorporate multiple variables
- Study is from the perspective of the provincial ministry of health (the payer) and does not adopt a societal perspective since much of the additional information required for that is not available
- Despite being set in one Canadian province, the use of intramuscular B₁₂ therapy is prevalent worldwide. Therefore, these results, while not directly generalizable to other jurisdictions, point to an economic argument for greater uptake of oral B₁₂ therapy which is likely consistent across other jurisdictions

BACKGROUND:

For over twenty years, oral vitamin B₁₂ has been referred to as “medicine’s best kept secret” [1]. Despite evidence of the effectiveness of oral B₁₂ therapy [2-7], intramuscular (IM) administration remains the most commonly prescribed route in North America [8].

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3 Approximately 5% of Canadians are B₁₂ deficient [9], with Framingham data suggesting that B₁₂
4 deficiency in community-dwelling adults age 67 and older may be as high as 12% [10].
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6 Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use
7 of antacids and other medications (metformin), inadequate animal product intake, and a
8 deficiency in intrinsic factor required for the absorption of cobalamin from the gut [11-12]. While
9 the absorbability of oral B₁₂ has been questioned, a number of studies have reported successful
10 results with oral therapy including treatment in patients with pernicious anemia or bowel
11 resection [4, 5, 13]. Since 1% of orally-ingested B₁₂ is absorbed via passive diffusion
12 independent of the presence of intrinsic factor [7], daily oral doses of 1000 mcg or more are
13 considered sufficient to meet daily requirements [14] even in patients with insufficient intrinsic
14 factor.
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29 While oral tablets often cost more to acquire than B₁₂ injection solution, the costs associated
30 with administering the injections in the form of health professionals' time and resources can be
31 significant. A 2001 cost study estimated that between \$2.9-17.6 million could be saved over 5
32 years in the province of Ontario if elderly patients on IM B₁₂ were switched to oral therapy [15].
33 In addition, a British study estimated that 2000 nursing hours are required to provide one year of
34 injections to 492 patients in their homes [16]. Across Canada, only Nova Scotia, Northwest
35 Territories, Yukon, and the Non-Insured Health Benefits program for First Nations and Inuit
36 consider oral B₁₂ tablets to be a benefit in their provincial drug formularies, while all provinces
37 and territories cover the injectable product.
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51 The objective of this study is to estimate the cost savings of treatment using daily oral vitamin
52 B₁₂ supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular
53 injections in Alberta seniors over the age of 65 who are currently using B₁₂ injection. Such a
54 study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to
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3 renew discussion about the best allocation of limited healthcare resources and whether oral B₁₂
4 should be covered by all Canadian provincial formularies.
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10 **METHODS:**
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14 **Study Type:** A cost-minimization analysis (CMA) was performed wherein alternatives compared
15 are considered to be equivalent in terms of factors that are relevant to the decision such as
16 efficacy and tolerability, so the lowest cost alternative is selected [17]. While a major
17 assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75
18 patients on IM therapy) [2-4] and two prospective case series of 87 patients switching from IM to
19 oral therapy [5, 7] have concluded that the oral route is as clinically effective as the
20 intramuscular route. Across both case series, no patients switched from IM to oral therapy
21 required a switch back to IM replacement as a result of therapeutic failure. Costs were modeled
22 over a period of five years, and the perspective of the Alberta Ministry of Health was adopted for
23 this study.
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38 **Setting / Patients:** The study population consists of individuals aged 65 or older with an Alberta
39 Health Care number receiving IM B₁₂ therapy. The number of Alberta seniors dispensed
40 injectable B₁₂ over a 1-year period (January-December 2012) was determined from prescription
41 dispensing records collected by IMS Brogan [18].
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49 **Primary Outcome:** Cost-savings achievable by the province of Alberta if patients aged ≥65 and
50 currently receiving IM B₁₂ therapy are switched to oral therapy. Cost savings are estimated in
51 Canadian currency.
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57 **Cost Determination:**
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3 Cost of B₁₂ Tablets: The suggested retail price of Swiss Naturals[®], Jamieson[®], and Nature's
4 Bounty[®] brands of 1000 mcg B₁₂ tablets were obtained from the manufacturers and averaged to
5 obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing
6 products with an acquisition cost of ≤\$74.99 is \$11.93 (consists of \$10.22 professional fee and
7 \$1.71 inventory allowance) [19].
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12 Quantity of B₁₂ Tablets and Professional Fees: It was assumed that patients would receive a
13 three-month supply with each fill, therefore amassing four professional fees annually and 365
14 tablets. Albertans age 65 and older are automatically enrolled into a 'Coverage for Seniors'
15 program, where the patient co-pay is 30% of the cost to a maximum of \$25 [20]. Since this study
16 assumes the perspective of the provincial Ministry of Health, the payer is assumed to cover 70%
17 of the total drug cost. Despite being a non-prescription product, sales tax was not applied since
18 such tablets would be dispensed through the pharmacy as a tax-free product similar to a
19 prescription drug.
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36 Cost of B₁₂ Injection: Parenteral B₁₂ in Alberta is available in 10 mL multi-dose vials at a
37 concentration of 1000 mcg/mL. The cost per mL for the two products currently available in
38 Alberta (DIN 00521515 and DIN 01987003) were determined from the Alberta Health Drug
39 Benefit List [21]. In Alberta, the total charge allowable for injectable drugs other than insulin is
40 5/3 of the product's acquisition cost [19]. Therefore, with an acquisition cost of \$4.50 per vial of
41 parenteral B₁₂, the total charge allowed – including the drug and professional fee – cannot
42 exceed \$7.50, or \$0.75 per dose.
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53 Quantity of B₁₂ injection: At the usual dosage of 1000 mcg/month, one vial contains a ten-month
54 supply of drug. Therefore, 1.2 vials would be required for a one-year supply.
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3 Cost of Additional Laboratory Monitoring: Costs for the laboratory analyses were obtained from
4 Alberta Health Services, laboratory technicians' time to draw and analyze the blood samples
5 were estimated by consulting with practicing laboratory technicians, and laboratory technician
6 wages were obtained from a Government of Alberta occupational survey [22] with a 20% fringe
7 benefit applied.
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16 Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we
17 assumed that patients to be switched from IM to oral B₁₂ would receive a baseline complete
18 blood count and serum B₁₂ prior to the switch, repeated once after the switch to confirm
19 effectiveness. It was assumed that this additional monitoring would occur only upon switch from
20 IM to oral therapy, with long-term monitoring occurring at the same rate as if the patient had
21 remained on IM injections, therefore representing no additional cost of oral therapy over IM
22 therapy following the initial switch.
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33 Cost of Injection Administration: Currently, physicians, nurses, and pharmacists are authorized
34 to administer B₁₂ by intramuscular injection in Alberta. Fees for physician office administration of
35 injections and pharmacist administration of injections are provided in Table 1.
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42 Quantity of Injection Administrations: It is unknown the proportion of patients on IM B₁₂ therapy
43 receiving their monthly injections from their physician's office or their pharmacy. For the purpose
44 of the study, based on the experience of the authors including a practicing pharmacist and
45 family physician, it was assumed that 25% of all B₁₂ injections are administered in a community
46 pharmacy with the remainder administered in a medical clinic.
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55 Cost of Additional Physician Visits: The current cost for a standard family physician consultation
56 visit in Alberta of \$35.91 was utilized in the model.
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5 Quantity of Additional Physician Visits: Based on available administrative data, we were unable
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7 to determine the number of additional physician visits received by and billed for patients on IM
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9 versus oral B₁₂ supplementation apart from simply the administration of the injection in the
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11 medical clinic. For the base case scenario, we assumed that 10% of injections administered in a
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13 physician's office also included a billed physician consultation which would not have occurred if
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15 the patient were not on IM B₁₂, and have explored other scenarios in sensitivity analyses as
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17 described below.
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20 21 22 **Model Assumptions:**

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26 A number of assumptions were made with the model in addition to those previously described. It
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28 was assumed that patients on oral B₁₂ therapy were able to self-administer the medication, and
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30 if assistance was required, it was assumed that they already required this assistance for other
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32 medications rather than solely for B₁₂ tablets. Since B₁₂ tablets can be taken concurrently with
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34 other medications, it was not assumed that additional assistance would be needed if oral B₁₂
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36 were added to their medication regimen. The cost of supplies to administer the intramuscular
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38 injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded
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40 from the model as these are relatively inexpensive and were not felt to significantly contribute to
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42 the overall cost of the injectable product.
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46 47 **Discounting:**

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52 Consistent with CADTH guidelines for the economic evaluation of health technologies [23], a
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54 discount rate of 5% for outcomes occurring after one year was applied to the reference case,
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56 with sensitivity analyses performed around this value as described below.
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Sensitivity Analyses:

Multi-way sensitivity analysis was performed in the form of 10,000 Monte Carlo simulation iterations, adjusting for a number of variables. Model inputs and the probabilistic distributions used in the sensitivity analyses are presented in Table 1. The base case scenario was calculated using the expected value for each variable and assumed a 10% rate of additional physician consultations for patients on intramuscular versus oral therapy.

Table 1. Expected Values and Distribution Parameters for the Deterministic Model and Probabilistic Sensitivity Analyses

Parameter	Expected Value \pm SE	Distribution
Study population	28,252 \pm 10%	Gamma
Cost per B ₁₂ tablet	\$0.16 \pm 0.008	Gamma
Professional Fee for Dispensing Tablets [19]	\$11.93	--
Cost per B ₁₂ injectable dose [19-21]	\$0.75	--
Cost for CBC and serum B ₁₂ analyses*	\$6.50	--
Laboratory technician time for blood sample draw and analyses (hours)*	0.75 (range 0.25-1)	Triangular
Laboratory technician wage and benefits [22]*	\$44.60 (range \$35.82-\$51.41)	Triangular
Fee for administration of intramuscular injection in a physician's office [24]	\$10.30	--
Cost for physician consultation visit [24]	\$35.91	--
Fee for administration of intramuscular injection in a pharmacy [25]	\$20.00	--

- SE=Standard Error; CBC=Complete blood count
- * indicates parameter only included in year 1 of the model
- Normal distribution samples values probabilistically from a normal curve with specified mean (expected value) and standard error. Triangular distribution samples values probabilistically within the range specified, with increasing probability as values near the expected value.

Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office

consultations during injection visits, the analyses were repeated for rates of 0% and 25%.

Discounting rates of 0% and 3% were also tested in sensitivity analysis.

RESULTS:

Estimated five-year cost savings associated with switching all Alberta seniors currently receiving injectable B₁₂ to oral therapy is \$13,975,883. Base scenario and sensitivity analysis results are presented in Table 2. Our model found that even if no additional physician visits were billed for among patients receiving IM therapy, over \$8 million could be saved from reduced administration costs alone.

Table 2. Model Results Over 5 Years

Proportion In-Office Injections Including a Fee for a Physician Visit	Discounting Rate for Years 2-5	Mean Cost Saving For Payer	Mean Cost Saving per Patient
Reference Case			
10%	5%	\$13,975,883	\$494.69
Sensitivity Analyses			
0%	0%	\$9,564,224	\$338.53
0%	3%	\$8,878,728	\$314.27
0%	5%	\$8,444,346	\$298.89
10%	0%	\$15,677,500	\$554.92
10%	3%	\$14,635,912	\$518.05
25%	0%	\$24,784,224	\$877.26
25%	3%	\$23,212,469	\$821.62
25%	5%	\$22,216,488	\$786.37

Due to the additional laboratory monitoring performed in the year of the change from IM to oral therapy, the model found the switch to be moderately cost-effective in the first year, with larger

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3 savings realized in years 2-5. For the base scenario, cost savings in year 1 were estimated at
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5 \$48.34 (SD \$8.58) per patient, increasing to \$126.55 (SD \$2.04) in year 2. Over 5 years,
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7 average cost-savings per patient was estimated at \$494.69.
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11 **DISCUSSION:**

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16 Over five years, the province of Alberta can be expected to free nearly \$14 million in healthcare
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18 costs if all seniors over the age of 65 currently receiving IM B₁₂ are switched to oral tablets.
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21 Despite evidence confirming that sufficient B₁₂ is absorbed by passive diffusion at a dose of
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23 1000 mcg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal
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25 disease [12], the intramuscular route continues to be commonly prescribed. With high health
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27 professional workloads and increasingly restricted healthcare budgets, a switch from IM to oral
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29 therapy will not only free health professional resources to see patients at greater need, but can
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31 also result in cost-savings for reinvestment into other needed services.
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36 The option of oral supplementation is well received by patients. A Canadian study by Kwong *et*
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38 *al.* found that 73% of patients receiving B₁₂ injections were willing to try oral B₁₂, and of those
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40 who tried the oral therapy, 71% wished to permanently remain on oral therapy [7]. Travel
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42 inconveniences were the most common reason for preferring the oral route. The authors
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44 concluded that oral therapy would decrease physician burden, increase patient control over
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46 therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding
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48 injections is unknown in adult patients, previous research has suggested that patients with
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50 diabetes value a reduced injection burden as much as they value disease control [26].
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53 Therefore, if a societal perspective including utility were considered, it is likely that the benefit of
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55 switching patients from IM to oral therapy would be even greater.
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3 A number of assumptions employed in the model have the potential to alter the results in either
4 direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy
5 rather than monthly refills, which would be expected to underestimate the cost-saving potential
6 of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have
7 also occurred as a result of calculating tablet cost based on non-generic products at higher
8 costs per tablet. Home care costs for the administration of B₁₂ injections in home-bound patients
9 was not included since the proportion of patients receiving in-home injections was unknown,
10 and it was assumed that these injections would be administered in conjunction with a regular
11 visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits
12 are indeed being performed for B₁₂ injections, then the savings of switching to oral B₁₂ would
13 obviously be greater. Importantly, the model also assumed that all patients making the switch to
14 oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore
15 representing maximum saving potential. This assumption is consistent with previously published
16 randomized controlled trials and case series reporting treatment success across all patients
17 studied [2-7].
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38 Direct comparison between our model and the results of the 2001 cost-saving paper cannot be
39 performed due to differing model assumptions and available data. Overall, both models report
40 significant cost-saving potential of the switch from the perspective of a government payer over
41 five years. However, due to higher current professional fees for injection administration, our
42 model found overall cost-savings even if no additional physician visits occurred for patients
43 receiving B₁₂ injections, whereas the previous study found a break-even point when 16.3% of
44 additional physician visits were avoided.
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55 The use of cost-minimization analysis is controversial as it assumes equal efficacy and
56 tolerability between the two options being compared; however, we feel this assumption is
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3 justifiable based on published data comparing the oral and intramuscular routes [2-7]. However,
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5 the total number of patients studied in the randomized trials (total n=141 across 3 studies) and
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7 case series (n=87) remains relatively small and doses employed across each study differed.
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9 Further research on a larger population, comparing standard-dose IM therapy to standard-dose
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11 oral therapy is therefore recommended and is currently being planned. Additionally, payers
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13 considering adding oral B₁₂ tablets to their formularies should consider allowing for the coverage
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15 of intramuscular therapy in the event of documented treatment failure on oral supplementation,
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17 until larger-scale studies confirming equivalence are conducted. Indeed, a planned randomized
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19 controlled trial of 320 patients age ≥65 in Spain will be directly comparing oral to IM B₁₂ and is
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21 expected to examine non-inferiority of oral therapy over one year (clinicaltrials.gov
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23 NCT01476007).
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29 Overall, our model estimates that \$8-24 million in cost-savings can be realized over five years if
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31 all Alberta seniors currently receiving IM vitamin B₁₂ are switched to oral therapy. Within closed
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33 systems like universal healthcare, this is unlikely to represent true cost savings, but rather room
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35 for re-allocation of resources to other health system needs. With an aging population and
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37 increasing rates of chronic disease, switching of patients from IM to oral vitamin B₁₂
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39 replacement appears to be not only clinically efficacious, but also an effective use of limited
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41 healthcare resources.
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57 Solutions).
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REFERENCES

1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. *JAMA* 1991;**265**:94-5.
2. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998;**92**(4):1191-1198.
3. Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective, randomized, open-label study. *Clin Ther* 2003;**25**(12):3124-3134.
4. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, et al. Comparing the Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-Label, Parallel-Group Study. *Clin Ther* 2011;**33**(3):358-71.
5. Nyholm E, Turpin P, Swain D, Cunningham B, Daly S, Nightingale P, et al. Oral vitamin B12 can change our practice. *Postgrad Med J* 2003;**79**:218-220.
6. Vidal-Alaball J, Butler C, Cannings-John R, Goringe A, Hood K, McCaddon A, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD004655. DOI:10..1002/14651858.CD004655.pub2.
7. Kwong JC, Carr D, Dhalla IA, Tom-Kun D, Upshur REG. Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. *BMC Fam Pract* 2005;**6**:8.
8. Graham ID, Jette N, Tetroe J, Robinson N, Milne S, Mitchell SL. Oral cobalamin remains medicine's best kept secret. *Archives of Gerontology and Geriatrics* 2007;**44**(1):49-59.

- 1
2
3 9. MacFarlane AJ, Greene-Finestone LS, Shi Y. Vitamin B-12 and homocysteine status in a
4 folate-replete population: results from the Canadian Health Measures Survey. *Am J Clin*
5
6 *Nutr* 2011;**94**:1079-87.
- 7
8
9
10 10. Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of cobalamin
11
12 deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;**60**:2-11.
- 13
14 11. de Jager J, Kooy A, Lehert P, Wulffele MG, van der Kolk J, Bets D, et al. Long term
15
16 treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency:
17
18 randomized placebo controlled trial. *Br Med J* 2010;**340**:c2181.
- 19
20 12. Andrès E, Vidal-Alaball J, Federici L, Henoun Loukili N, Zimmer J, Kaltenbach G. Clinical
21
22 aspects of cobalamin deficiency in elderly patients. Epidemiology, causes, clinical
23
24 manifestations, and treatment with special focus on oral cobalamin therapy. *Eur J Int Med*
25
26 2007;**18**:456-62.
- 27
28 13. Andrès E, Federici L, Affenberger S, Vidal-Alaball J, Henoun Loukili N, et al. B12 deficiency:
29
30 A look beyond pernicious anemia. *J Fam Pract* 2007;**56**(7):537-42.
- 31
32 14. Health Canada. Dietary Reference Intakes: Reference Values for Vitamins. Accessed 17
33
34 May 2012 at <http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref_vitam_tbl-eng.php>.
- 35
36 15. van Walraven CG, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements:
37
38 How much money could be saved by switching from injections to pills? *Can Med Assoc J*
39
40 2001;**47**:79-86.
- 41
42 16. Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district
43
44 nurse. *BMJ* 1985;**270**:1254-1255.
- 45
46 17. Drummond MF, Sculpher MJ, Torrance G, O'Brien B, Stoddart G. *Methods for the Economic*
47
48 *Evaluation of Health Care Programmes*. 3rd ed. New York: Oxford University Press; 2005.
- 49
50 18. IMS Brogan LRx database, January 2013 and Compuscript audit, January 2013.
- 51
52 19. Alberta Health. Pharmacy fee reimbursement. Retrieved from:
53
54
55
56
57 <http://www.health.alberta.ca/services/pharmacy-fee-reimbursement.html>
58
59
60

- 1
2
3 20. Alberta Health. Coverage for Seniors. Retrieved from:
4
5 <http://www.health.alberta.ca/services/drugs-seniors.html>
6
7
8 21. Alberta Health. Interactive Drug Benefit List. Retrieved from:
9
10 <https://idbl.ab.bluecross.ca/idbl/load.do>
11
12 22. Government of Alberta. 2011 Alberta Wage and Salary Data – Medical Laboratory
13
14 Technologist. Retrieved from:
15
16 http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140
17
18
19
20 23. *Guidelines for the economic evaluation of health technologies: Canada* [3rd Edition].
21
22 Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
23
24 24. Alberta Health Care Insurance Plan. Medical Price List as of 01 April 2012. Retrieved from:
25
26 <http://www.health.alberta.ca/documents/SOMB-Medical-Prices-2012-04.pdf>
27
28
29 25. Alberta Health. Compensation for Pharmacy Services, July 2012. Retrieved from:
30
31 <http://www.health.alberta.ca/documents/Pharmacy-Services-Compensation-2012.pdf>
32
33
34 26. Hauber AB, Johnson FR, Sauriol L, Lescrauwaet B. Risking health to avoid injections:
35
36 Preferences of Canadians with type 2 diabetes. *Diabetes Care* 2005;28(9):2243-5.
37
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EVEREST Statement

	Study section	Additional remarks
Study design		
(1) The research question is stated	Background	
(2) The economic importance of the research question is stated	Background	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods (Study Type); Discussion	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Background; Methods	
(5) The alternatives being compared are clearly described	Methods (Cost Determination)	
(6) The form of economic evaluation used is stated	Methods (Study Type)	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Methods; Discussion	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods (Study Type)	
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A (based on multiple studies)	3 randomized controlled trials and 2 prospective case series
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods (Primary Outcome)	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	Methods (Setting/Patients)	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods (Cost Determination)	
(17) Methods for the estimation of quantities and unit costs are described	Methods (Cost Determination)	
(18) Currency and price data are recorded	Methods (Primary Outcome)	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	

(20) Details of any model used are given	Methods (Model Assumptions, Discounting, Sensitivity Analyses)	
(21) The choice of model used and the key parameters on which it is based are justified	Methods (Study Type); Discussion	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods (Study Type)	
(23) The discount rate(s) is stated	Methods (Discounting)	
(24) The choice of rate(s) is justified	Methods (Discounting)	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods (Sensitivity Analyses)	
(28) The choice of variables for sensitivity analysis is justified	Methods (Sensitivity Analyses)	
(29) The ranges over which the variables are varied are stated	Table 1	
(30) Relevant alternatives are compared	Introduction	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	N/A	
(33) The answer to the study question is given	Results; Discussion	
(34) Conclusions follow from the data reported	Discussion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	



Should Vitamin B12 Tablets be Included in More Canadian Drug Formularies? An Economic Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular Vitamin B12 Maintenance Therapy for Alberta Seniors

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3 Should Vitamin B₁₂ Tablets be Included in More Canadian Drug Formularies? An Economic
4
5 Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular
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7 Vitamin B₁₂ Maintenance Therapy for Alberta Seniors
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49 **Keywords:** Cost analysis, healthcare costs, vitamin B₁₂ deficiency
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53 **Word Count:** 2881
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ABSTRACT:

Objectives: The aim of this study is to estimate the cost-savings attainable if all patients aged ≥ 65 in Alberta, Canada, currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

Setting: Primary care setting in Alberta, Canada.

Participants: Seniors age 65 and older currently receiving intramuscular vitamin B₁₂ therapy.

Intervention: Oral vitamin B₁₂ therapy at 1000 mcg per day versus intramuscular therapy at 1000 mcg per month.

Primary and Secondary Outcome Measures: Cost-saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring, and physician visit fees.

Results: Over 5 years, if all Albertans age 65 and older who currently receive intramuscular B₁₂ are switched to oral therapy, our model found that CAD \$13,975,883 can be saved. Even if no additional physician visits are billed for among patients receiving IM therapy, \$8,444,346 could be saved from reduced administration costs alone.

Conclusions: Oral B₁₂ therapy has been shown to be an effective therapeutic option for patients with vitamin B₁₂ deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation.

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3 To ensure judicious use of limited health resources, clinicians and formulary committees are
4 encouraged to adopt oral B₁₂ therapy as a clinically- and cost-effective first line therapy for
5 vitamin B₁₂ deficiency.
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11 **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

- 14 • Minimal assumptions built into the model, as exact costs and the exact number of
15 eligible residents comprising the population were available
 - 16 • Three randomized controlled trials and two prospective case series support our use of a
17 cost-minimization analysis approach
 - 18 • Comprehensive sensitivity analyses employed using Monte Carlo simulation to
19 incorporate multiple variables
 - 20 • Study is from the perspective of the provincial ministry of health (the payer) and does not
21 adopt a societal perspective since much of the additional information required for that is
22 not available
 - 23 • Despite being set in one Canadian province, the use of intramuscular B₁₂ therapy is
24 prevalent worldwide. Therefore, these results, while not directly generalizable to other
25 jurisdictions, point to an economic argument for greater uptake of oral B₁₂ therapy which
26 is likely consistent across other jurisdictions
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BACKGROUND:

For over twenty years, oral vitamin B₁₂ has been referred to as “medicine’s best kept secret” [1]. Despite evidence of the effectiveness of oral B₁₂ therapy [2-8], intramuscular (IM) administration remains the most commonly prescribed route in North America [9].

Approximately 5% of Canadians are B₁₂ deficient [10], with Framingham data suggesting that B₁₂ deficiency in community-dwelling adults age 67 and older may be as high as 12% [11]. Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use of antacids and other medications (metformin), inadequate animal product intake, and a deficiency in intrinsic factor required for the absorption of cobalamin from the gut [12-13]. While the absorbability of oral B₁₂ has been questioned, a number of studies have reported successful results with oral therapy including treatment in patients with pernicious anemia or bowel resection [4, 5, 8, 14]. Since 1% of orally-ingested B₁₂ is absorbed via passive diffusion independent of the presence of intrinsic factor [7], daily oral doses of 1000 mcg or more are considered sufficient to meet daily requirements [15] even in patients with insufficient intrinsic factor.

While oral tablets often cost more to acquire than B₁₂ injection solution, the costs associated with administering the injections in the form of health professionals’ time and resources can be significant. A 2001 cost study estimated that between \$2.9-17.6 million could be saved over 5 years in the province of Ontario if elderly patients on IM B₁₂ were switched to oral therapy [16]. In addition, a British study estimated that 2000 nursing hours are required to provide one year of injections to 492 patients in their homes [17]. Across Canada, only Nova Scotia, Northwest Territories, Yukon, and the Non-Insured Health Benefits program for First Nations and Inuit

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2
3 consider oral B₁₂ tablets to be a benefit in their provincial drug formularies, while all provinces
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5 and territories cover the injectable product.
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10 The objective of this study is to estimate the cost savings of treatment using daily oral vitamin
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12 B₁₂ supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular
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14 injections in Alberta seniors over the age of 65 who are currently using B₁₂ injection. Such a
15
16 study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to
17
18 renew discussion about the best allocation of limited healthcare resources and whether oral B₁₂
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20 should be covered by all Canadian provincial formularies.
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23 24 25 **METHODS:**

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29 **Study Type:** A cost-minimization analysis (CMA) was performed wherein alternatives compared
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31 are considered to be equivalent in terms of factors that are relevant to the decision such as
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33 efficacy and tolerability, so the lowest cost alternative is selected [18]. While a major
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35 assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75
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37 patients on IM therapy) [2-4] and three prospective case series of 151 patients switching from
38
39 IM to oral therapy [5, 7, 8] have concluded that the oral route is as clinically effective as the
40
41 intramuscular route. Across all case series, no patients switched from IM to oral therapy
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43 required a switch back to IM replacement as a result of therapeutic failure. Costs were modeled
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45 over a period of five years, and the perspective of the Alberta Ministry of Health was adopted for
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47 this study.
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53 **Setting / Patients:** The study population consists of individuals aged 65 or older with an Alberta
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55 Health Care number receiving IM B₁₂ therapy. The number of Alberta seniors dispensed
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3 injectable B₁₂ over a 1-year period (January-December 2012) was determined from prescription
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5 dispensing records collected by IMS Brogan [19].
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10 **Primary Outcome:** Cost-savings achievable by the province of Alberta if patients aged ≥65 and
11 currently receiving IM B₁₂ therapy are switched to oral therapy. Cost savings are estimated in
12 Canadian currency.
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18 **Cost Determination:**

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20 All costs are reported in Canadian dollars.
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25 Cost of B₁₂ Tablets: The suggested retail price of Swiss Naturals[®], Jamieson[®], and Nature's
26 Bounty[®] brands of 1000 mcg B₁₂ tablets were obtained from the manufacturers and averaged to
27 obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing
28 products with an acquisition cost of ≤\$74.99 is \$11.93 (consists of \$10.22 professional fee and
29 \$1.71 inventory allowance) [20].
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38 Quantity of B₁₂ Tablets and Professional Fees: It was assumed that patients would receive a
39 three-month supply with each fill, therefore amassing four professional fees annually and 365
40 tablets. Albertans age 65 and older are automatically enrolled into a 'Coverage for Seniors'
41 program, where the patient co-pay is 30% of the cost to a maximum of \$25 [21]. Since this study
42 assumes the perspective of the provincial Ministry of Health, the payer is assumed to cover 70%
43 of the total drug cost. Despite being a non-prescription product, sales tax was not applied since
44 such tablets would be dispensed through the pharmacy as a tax-free product similar to a
45 prescription drug.
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3 Cost of B₁₂ Injection: Parenteral B₁₂ in Alberta is available in 10 mL multi-dose vials at a
4 concentration of 1000 mcg/mL. The cost per mL for the two products currently available in
5 Alberta (DIN 00521515 and DIN 01987003) were determined from the Alberta Health Drug
6 Benefit List [22]. In Alberta, the total charge allowable for injectable drugs other than insulin is
7 5/3 of the product's acquisition cost [20]. Therefore, with an acquisition cost of \$4.50 per vial of
8 parenteral B₁₂, the total charge allowed – including the drug and professional fee – cannot
9 exceed \$7.50, or \$0.75 per dose.
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20 Quantity of B₁₂ injection: At the usual dosage of 1000 mcg/month, one vial contains a ten-month
21 supply of drug. Therefore, 1.2 vials would be required for a one-year supply.
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27 Cost of Additional Laboratory Monitoring: Costs for the laboratory analyses were obtained from
28 Alberta Health Services, laboratory technicians' time to draw and analyze the blood samples
29 were estimated by consulting with practicing laboratory technicians, and laboratory technician
30 wages were obtained from a Government of Alberta occupational survey [23] with a 20% fringe
31 benefit applied.
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40 Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we
41 assumed that patients to be switched from IM to oral B₁₂ would receive a baseline complete
42 blood count and serum B₁₂ prior to the switch, repeated once after the switch to confirm
43 effectiveness. It was assumed that this additional monitoring would occur only upon switch from
44 IM to oral therapy, with long-term monitoring occurring at the same rate as if the patient had
45 remained on IM injections, therefore representing no additional cost of oral therapy over IM
46 therapy following the initial switch.
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3 Cost of Injection Administration: Currently, physicians, nurses, and pharmacists are authorized
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5 to administer B₁₂ by intramuscular injection in Alberta. Fees for physician office administration of
6
7 injections and pharmacist administration of injections are provided in Table 1.
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11 Quantity of Injection Administrations: It is unknown the proportion of patients on IM B₁₂ therapy
12
13 receiving their monthly injections from their physician's office or their pharmacy. For the purpose
14
15 of the study, based on the experience of the authors including a practicing pharmacist and
16
17 family physician, it was assumed that 25% of all B₁₂ injections are administered in a community
18
19 pharmacy with the remainder administered in a medical clinic.
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25 Cost of Additional Physician Visits: The current cost for a standard family physician consultation
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27 visit in Alberta of \$35.91 was utilized in the model.
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31 Quantity of Additional Physician Visits: Based on available administrative data, we were unable
32
33 to determine the number of additional physician visits received by and billed for patients on IM
34
35 versus oral B₁₂ supplementation apart from simply the administration of the injection in the
36
37 medical clinic. For the base case scenario, we assumed that 10% of injections administered in a
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39 physician's office also included a billed physician consultation which would not have occurred if
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41 the patient were not on IM B₁₂, and have explored other scenarios in sensitivity analyses as
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43 described below.
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49 **Model Assumptions:**

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52 A number of assumptions were made with the model in addition to those previously described. It
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54 was assumed that patients on oral B₁₂ therapy were able to self-administer the medication, and
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56 if assistance was required, it was assumed that they already required this assistance for other
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3 medications rather than solely for B₁₂ tablets. Since B₁₂ tablets can be taken concurrently with
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5 other medications, it was not assumed that additional assistance would be needed if oral B₁₂
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7 were added to their medication regimen. The cost of supplies to administer the intramuscular
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9 injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded
10
11 from the model as these are relatively inexpensive and were not felt to significantly contribute to
12
13 the overall cost of the injectable product.
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16 17 18 **Discounting:** 19

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22 Consistent with CADTH guidelines for the economic evaluation of health technologies [24], a
23
24 discount rate of 5% for outcomes occurring after one year was applied to the reference case,
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26 with sensitivity analyses performed around this value as described below.
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30 31 **Sensitivity Analyses:** 32

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35 Multi-way sensitivity analysis was performed in the form of 10,000 Monte Carlo simulation
36
37 iterations, adjusting for a number of variables. Model inputs and the probabilistic distributions
38
39 used in the sensitivity analyses are presented in Table 1. The base case scenario was
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41 calculated using the expected value for each variable and assumed a 10% rate of additional
42
43 physician consultations for patients on intramuscular versus oral therapy.
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49 **Table 1. Expected Values and Distribution Parameters for the Deterministic Model and**
50 **Probabilistic Sensitivity Analyses**
51

52 Parameter	53 Expected Value ± SE	54 Distribution
55 Study population	28,252 ± 10%	Gamma
56 Cost per B ₁₂ tablet	\$0.16 ± 0.008	Gamma
57 Professional Fee for Dispensing Tablets [20]	\$11.93	--

Cost per B ₁₂ injectable dose [20-22]	\$0.75	--
Cost for CBC and serum B ₁₂ analyses*	\$6.50	--
Laboratory technician time for blood sample draw and analyses (hours)*	0.75 (range 0.25-1)	Triangular
Laboratory technician wage and benefits [23]*	\$44.60 (range \$35.82-\$51.41)	Triangular
Fee for administration of intramuscular injection in a physician's office [25]	\$10.30	--
Cost for physician consultation visit [25]	\$35.91	--
Fee for administration of intramuscular injection in a pharmacy [26]	\$20.00	--

- SE=Standard Error; CBC=Complete blood count
- * indicates parameter only included in year 1 of the model
- Normal distribution samples values probabilistically from a normal curve with specified mean (expected value) and standard error. Triangular distribution samples values probabilistically within the range specified, with increasing probability as values near the expected value.

Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office consultations during injection visits, the analyses were repeated for rates of 0% and 25%. Discounting rates of 0% and 3% were also tested in sensitivity analysis.

RESULTS:

Estimated five-year cost savings associated with switching all Alberta seniors currently receiving injectable B₁₂ to oral therapy is \$13,975,883. Base scenario and sensitivity analysis results are presented in Table 2. Our model found that even if no additional physician visits were billed for among patients receiving IM therapy, over \$8 million could be saved from reduced administration costs alone.

Table 2. Model Results Over 5 Years

Proportion In-Office Injections Including a Fee for	Discounting Rate for Years 2-5	Mean Cost Saving For Payer	Mean Cost Saving per Patient
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a Physician Visit			
Reference Case			
10%	5%	\$13,975,883	\$494.69
Sensitivity Analyses			
0%	0%	\$9,564,224	\$338.53
0%	3%	\$8,878,728	\$314.27
0%	5%	\$8,444,346	\$298.89
10%	0%	\$15,677,500	\$554.92
10%	3%	\$14,635,912	\$518.05
25%	0%	\$24,784,224	\$877.26
25%	3%	\$23,212,469	\$821.62
25%	5%	\$22,216,488	\$786.37

Due to the additional laboratory monitoring performed in the year of the change from IM to oral therapy, the model found the switch to be moderately cost-effective in the first year, with larger savings realized in years 2-5. For the base scenario, cost savings in year 1 were estimated at \$48.34 (SD \$8.58) per patient, increasing to \$126.55 (SD \$2.04) in year 2. Over 5 years, average cost-savings per patient was estimated at \$494.69.

DISCUSSION:

Over five years, the province of Alberta can be expected to free nearly \$14 million in healthcare costs if all seniors over the age of 65 currently receiving IM B₁₂ are switched to oral tablets.

Despite evidence confirming that sufficient B₁₂ is absorbed by passive diffusion at a dose of 1000 mcg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal disease [13], the intramuscular route continues to be commonly prescribed. With high health professional workloads and increasingly restricted healthcare budgets, a switch from IM to oral therapy will not only free health professional resources to see patients at greater need, but can also result in cost-savings for reinvestment into other needed services.

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5 The option of oral supplementation is well received by patients. A Canadian study by Kwong *et*
6 *al.* found that 73% of patients receiving B₁₂ injections were willing to try oral B₁₂, and of those
7 who tried the oral therapy, 71% wished to permanently remain on oral therapy [7]. Travel
8 inconveniences were the most common reason for preferring the oral route. The authors
9 concluded that oral therapy would decrease physician burden, increase patient control over
10 therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding
11 injections is unknown in adult patients, previous research has suggested that patients with
12 diabetes value a reduced injection burden as much as they value disease control [27].
13

14
15 Therefore, if a societal perspective including utility were considered, it is likely that the benefit of
16 switching patients from IM to oral therapy would be even greater. Furthermore, the elimination
17 of risk for injection site reactions following a switch to oral therapy represents another potential
18 benefit from the patient perspective.
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23
24 A number of assumptions employed in the model have the potential to alter the results in either
25 direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy
26 rather than monthly refills, which would be expected to underestimate the cost-saving potential
27 of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have
28 also occurred as a result of calculating tablet cost based on non-generic products at higher
29 costs per tablet. Home care costs for the administration of B₁₂ injections in home-bound patients
30 was not included since the proportion of patients receiving in-home injections was unknown,
31 and it was assumed that these injections would be administered in conjunction with a regular
32 visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits
33 are indeed being performed for B₁₂ injections, then the savings of switching to oral B₁₂ would
34 obviously be greater. Importantly, the model also assumed that all patients making the switch to
35 oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore
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3 representing maximum saving potential. This assumption is consistent with previously published
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5 randomized controlled trials and case series reporting treatment success across all patients
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7 studied [2-8]. Additionally, we assumed in the base scenario that additional laboratory
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9 monitoring is only required for the first year following the switch to oral therapy, with monitoring
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11 as usual for the remaining years. Considering that adherence to self-administered oral therapy
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13 may be lower than a healthcare professional-administered injection, even if an additional set of
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15 laboratory tests were performed each year for the 5-year term of the model, estimated cost
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17 savings would still amount to \$12 million.
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22 Direct comparison between our model and the results of the 2001 cost-saving paper cannot be
23
24 performed due to differing model assumptions and available data. Overall, both models report
25
26 significant cost-saving potential of the switch from the perspective of a government payer over
27
28 five years. However, due to higher current professional fees for injection administration, our
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30 model found overall cost-savings even if no additional physician visits occurred for patients
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32 receiving B₁₂ injections, whereas the previous study found a break-even point when 16.3% of
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34 additional physician visits were avoided.
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39 The use of cost-minimization analysis is controversial as it assumes equal efficacy and
40
41 tolerability between the two options being compared; however, we feel this assumption is
42
43 justifiable based on published data comparing the oral and intramuscular routes [2-8]. However,
44
45 the total number of patients studied in the randomized trials (total n=141 across 3 studies) and
46
47 case series (n=151) remains relatively small and doses employed across each study differed.
48
49 Further research on a larger population, comparing standard-dose IM therapy to standard-dose
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51 oral therapy is therefore recommended and is currently being planned. Additionally, payers
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53 considering adding oral B₁₂ tablets to their formularies should consider allowing for the coverage
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55 of intramuscular therapy in the event of documented treatment failure on oral supplementation,
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3 until larger-scale studies confirming equivalence are conducted, or allowing for short-term IM
4 therapy for patients with neurologic symptoms followed by oral maintenance therapy. Indeed, a
5 planned randomized controlled trial of 320 patients age ≥ 65 in Spain will be directly comparing
6 oral to IM B₁₂ and is expected to examine non-inferiority of oral therapy over one year
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12 (clinicaltrials.gov NCT01476007).
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16 Overall, our model estimates that \$8-24 million in cost-savings can be realized over five years if
17 all Alberta seniors currently receiving IM vitamin B₁₂ are switched to oral therapy. Within closed
18 systems like universal healthcare, this is unlikely to represent true cost savings, but rather room
19 for re-allocation of resources to other health system needs. With an aging population and
20 increasing rates of chronic disease, switching of patients from IM to oral vitamin B₁₂
21 replacement appears to be not only clinically efficacious, but also an effective use of limited
22 healthcare resources.
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4
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6
7 Canada, and the Interdisciplinary Chronic Disease Collaboration (funded by Alberta Innovates –
8
9 Health Solutions).
10

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13
14 **Contributorship Statement:** All authors (Dr. Houle, Dr. Kolber, and Dr. Chuck) contributed to
15
16 the design and analysis/interpretation of data, drafting of the article, and approval of the final
17
18 version.
19

20 **Competing Interests:** The authors declare no conflicts of interest related to the above work.
21
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24 **Data Sharing Statement:** There is no additional unpublished data related to this study.
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REFERENCES

1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. *JAMA* 1991;**265**:94-5.
2. Kuzminski AM, Del Giacco EJ, Allen RH, et al. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998;**92**(4):1191-1198.
3. Bolaman Z, Kadikoylu G, Yukselen V, et al. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective, randomized, open-label study. *Clin Ther* 2003;**25**(12):3124-3134.
4. Castelli MC, Friedman K, Sherry J, et al. Comparing the Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-Label, Parallel-Group Study. *Clin Ther* 2011;**33**(3):358-71.
5. Nyholm E, Turpin P, Swain D, et al. Oral vitamin B12 can change our practice. *Postgrad Med J* 2003;**79**:218-220.
6. Vidal-Alaball J, Butler C, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD004655. DOI:10.1002/14651858.CD004655.pub2.
7. Kwong JC, Carr D, Dhalla IA, et al. Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. *BMC Fam Pract* 2005;**6**:8.
8. Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. *Acta Med Scand* 1968;**184**:247-58.
9. Graham ID, Jette N, Tetroe J, et al. Oral cobalamin remains medicine's best kept secret. *Archives of Gerontology and Geriatrics* 2007;**44**(1):49-59.

10. MacFarlane AJ, Greene-Finestone LS, Shi Y. Vitamin B-12 and homocysteine status in a folate-replete population: results from the Canadian Health Measures Survey. *Am J Clin Nutr* 2011;**94**:1079-87.
11. Lindenbaum J, Rosenberg IH, Wilson PW, et al. Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;**60**:2-11.
12. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomized placebo controlled trial. *Br Med J* 2010;**340**:c2181.
13. Andrès E, Vidal-Alaball J, Federici L, et al. Clinical aspects of cobalamin deficiency in elderly patients. Epidemiology, causes, clinical manifestations, and treatment with special focus on oral cobalamin therapy. *Eur J Int Med* 2007;**18**:456-62.
14. Andrès E, Federici L, Affenberger S, et al. B12 deficiency: A look beyond pernicious anemia. *J Fam Pract* 2007;**56**(7):537-42.
15. Health Canada. Dietary Reference Intakes: Reference Values for Vitamins. Accessed 17 May 2012 at <http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref_vitam_tbl-eng.php>.
16. van Walraven CG, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements: How much money could be saved by switching from injections to pills? *Can Med Assoc J* 2001;**47**:79-86.
17. Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district nurse. *BMJ* 1985;**270**:1254-1255.
18. Drummond MF, Sculpher MJ, Torrance G, O'Brien B, et al. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. New York: Oxford University Press; 2005.
19. IMS Brogan LRx database, January 2013 and Compuscript audit, January 2013.
20. Alberta Health. Pharmacy fee reimbursement. Retrieved from:
<http://www.health.alberta.ca/services/pharmacy-fee-reimbursement.html>

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2
3 21. Alberta Health. Coverage for Seniors. Retrieved from:
4
5 <http://www.health.alberta.ca/services/drugs-seniors.html>
6
7
8 22. Alberta Health. Interactive Drug Benefit List. Retrieved from:
9
10 <https://idbl.ab.bluecross.ca/idbl/load.do>
11
12 23. Government of Alberta. 2011 Alberta Wage and Salary Data – Medical Laboratory
13
14 Technologist. Retrieved from:
15
16 http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140
17
18
19
20 24. *Guidelines for the economic evaluation of health technologies: Canada* [3rd Edition].
21
22 Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
23
24 25. Alberta Health Care Insurance Plan. Medical Price List as of 01 April 2012. Retrieved from:
25
26 <http://www.health.alberta.ca/documents/SOMB-Medical-Prices-2012-04.pdf>
27
28
29 26. Alberta Health. Compensation for Pharmacy Services, July 2012. Retrieved from:
30
31 <http://www.health.alberta.ca/documents/Pharmacy-Services-Compensation-2012.pdf>
32
33
34 27. Hauber AB, Johnson FR, Sauriol L, et al. Risking health to avoid injections: Preferences of
35
36 Canadians with type 2 diabetes. *Diabetes Care* 2005;28(9):2243-5.
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3 | Should Vitamin B₁₂ Tablets be Included in More Canadian Drug Formularies? An Economic
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5 | Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular
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7 | Vitamin B₁₂ Maintenance Therapy for Alberta Seniors
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49 **Keywords:** Cost analysis, healthcare costs, vitamin B₁₂ deficiency
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ABSTRACT:

Objectives: The aim of this study is to estimate the cost-savings attainable if all patients aged ≥ 65 in Alberta, Canada, and currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

Setting: Primary care setting in Alberta, Canada.

Participants: Seniors age 65 and older currently receiving intramuscular vitamin B₁₂ therapy.

Intervention: Oral vitamin B₁₂ therapy at 1000 mcg per day versus intramuscular therapy at 1000 mcg per month.

Primary and Secondary Outcome Measures: Cost-saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring, and physician visit fees.

Results: Over 5 years, if all Albertans age 65 and older who currently receive intramuscular B₁₂ are switched to oral therapy, our model found that CAD \$13,975,883 can be saved. Even if no additional physician visits are billed for among patients receiving IM therapy, \$8,444,346 could be saved from reduced administration costs alone.

Conclusions: Oral B₁₂ therapy has been shown to be an effective therapeutic option for patients with vitamin B₁₂ deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation.

To ensure judicious use of limited health resources, clinicians and formulary committees are encouraged to adopt oral B₁₂ therapy as a clinically- and cost-effective first line therapy for vitamin B₁₂ deficiency.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- Minimal assumptions built into the model, as exact costs and the exact number of eligible residents comprising the population were available
- Three randomized controlled trials and two prospective case series support our use of a cost-minimization analysis approach
- Comprehensive sensitivity analyses employed using Monte Carlo simulation to incorporate multiple variables
- Study is from the perspective of the provincial ministry of health (the payer) and does not adopt a societal perspective since much of the additional information required for that is not available
- Despite being set in one Canadian province, the use of intramuscular B₁₂ therapy is prevalent worldwide. Therefore, these results, while not directly generalizable to other jurisdictions, point to an economic argument for greater uptake of oral B₁₂ therapy which is likely consistent across other jurisdictions

BACKGROUND:

For over twenty years, oral vitamin B₁₂ has been referred to as “medicine’s best kept secret” [1].

Despite evidence of the effectiveness of oral B₁₂ therapy [2-78], intramuscular (IM) administration remains the most commonly prescribed route in North America [98].

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3 | Approximately 5% of Canadians are B₁₂ deficient [910], with Framingham data suggesting that
4 | B₁₂ deficiency in community-dwelling adults age 67 and older may be as high as 12% [4011].
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6 | Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use
7 | of antacids and other medications (metformin), inadequate animal product intake, and a
8 | deficiency in intrinsic factor required for the absorption of cobalamin from the gut [4412-132].
9 |
10 | While the absorbability of oral B₁₂ has been questioned, a number of studies have reported
11 | successful results with oral therapy including treatment in patients with pernicious anemia or
12 | bowel resection [4, 5, 8, 1314]. Since 1% of orally-ingested B₁₂ is absorbed via passive diffusion
13 | independent of the presence of intrinsic factor [7], daily oral doses of 1000 mcg or more are
14 | considered sufficient to meet daily requirements [4415] even in patients with insufficient intrinsic
15 | factor.
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29 | While oral tablets often cost more to acquire than B₁₂ injection solution, the costs associated
30 | with administering the injections in the form of health professionals' time and resources can be
31 | significant. A 2001 cost study estimated that between \$2.9-17.6 million could be saved over 5
32 | years in the province of Ontario if elderly patients on IM B₁₂ were switched to oral therapy
33 | [4516]. In addition, a British study estimated that 2000 nursing hours are required to provide one
34 | year of injections to 492 patients in their homes [4617]. Across Canada, only Nova Scotia,
35 | Northwest Territories, Yukon, and the Non-Insured Health Benefits program for First Nations
36 | and Inuit consider oral B₁₂ tablets to be a benefit in their provincial drug formularies, while all
37 | provinces and territories cover the injectable product.
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51 | The objective of this study is to estimate the cost savings of treatment using daily oral vitamin
52 | B₁₂ supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular
53 | injections in Alberta seniors over the age of 65 who are currently using B₁₂ injection. Such a
54 | study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to
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3 renew discussion about the best allocation of limited healthcare resources and whether oral B₁₂
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5 should be covered by all Canadian provincial formularies.
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9 10 **METHODS:**

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14 **Study Type:** A cost-minimization analysis (CMA) was performed wherein alternatives compared
15 are considered to be equivalent in terms of factors that are relevant to the decision such as
16 efficacy and tolerability, so the lowest cost alternative is selected [4718]. While a major
17 assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75
18 patients on IM therapy) [2-4] and threetwo prospective case series of 15187 patients switching
19 from IM to oral therapy [5, 7, 8] have concluded that the oral route is as clinically effective as the
20 intramuscular route. Across allboth case series, no patients switched from IM to oral therapy
21 required a switch back to IM replacement as a result of therapeutic failure. Costs were modeled
22 over a period of five years, and the perspective of the Alberta Ministry of Health was adopted for
23 this study.
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38 **Setting / Patients:** The study population consists of individuals aged 65 or older with an Alberta
39 Health Care number receiving IM B₁₂ therapy. The number of Alberta seniors dispensed
40 injectable B₁₂ over a 1-year period (January-December 2012) was determined from prescription
41 dispensing records collected by IMS Brogan [4819].
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49 **Primary Outcome:** Cost-savings achievable by the province of Alberta if patients aged ≥65 and
50 currently receiving IM B₁₂ therapy are switched to oral therapy. Cost savings are estimated in
51 Canadian currency.
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57 **Cost Determination:**
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3 All costs are reported in Canadian dollars.
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8 Cost of B₁₂ Tablets: The suggested retail price of Swiss Naturals[®], Jamieson[®], and Nature's
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10 Bounty[®] brands of 1000 mcg B₁₂ tablets were obtained from the manufacturers and averaged to
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12 obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing
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14 products with an acquisition cost of ≤\$74.99 is \$11.93 (consists of \$10.22 professional fee and
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16 \$1.71 inventory allowance) [2049].
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21 Quantity of B₁₂ Tablets and Professional Fees: It was assumed that patients would receive a
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23 three-month supply with each fill, therefore amassing four professional fees annually and 365
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25 tablets. Albertans age 65 and older are automatically enrolled into a 'Coverage for Seniors'
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27 program, where the patient co-pay is 30% of the cost to a maximum of \$25 [210]. Since this
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29 study assumes the perspective of the provincial Ministry of Health, the payer is assumed to
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31 cover 70% of the total drug cost. Despite being a non-prescription product, sales tax was not
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33 applied since such tablets would be dispensed through the pharmacy as a tax-free product
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35 similar to a prescription drug.
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40 Cost of B₁₂ Injection: Parenteral B₁₂ in Alberta is available in 10 mL multi-dose vials at a
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42 concentration of 1000 mcg/mL. The cost per mL for the two products currently available in
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44 Alberta (DIN 00521515 and DIN 01987003) were determined from the Alberta Health Drug
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46 Benefit List [224]. In Alberta, the total charge allowable for injectable drugs other than insulin is
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48 5/3 of the product's acquisition cost [2049]. Therefore, with an acquisition cost of \$4.50 per vial
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50 of parenteral B₁₂, the total charge allowed – including the drug and professional fee – cannot
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52 exceed \$7.50, or \$0.75 per dose.
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3 Quantity of B₁₂ injection: At the usual dosage of 1000 mcg/month, one vial contains a ten-month
4 supply of drug. Therefore, 1.2 vials would be required for a one-year supply.
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10 Cost of Additional Laboratory Monitoring: Costs for the laboratory analyses were obtained from
11 Alberta Health Services, laboratory technicians' time to draw and analyze the blood samples
12 were estimated by consulting with practicing laboratory technicians, and laboratory technician
13 wages were obtained from a Government of Alberta occupational survey [232] with a 20% fringe
14 benefit applied.
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22 Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we
23 assumed that patients to be switched from IM to oral B₁₂ would receive a baseline complete
24 blood count and serum B₁₂ prior to the switch, repeated once after the switch to confirm
25 effectiveness. It was assumed that this additional monitoring would occur only upon switch from
26 IM to oral therapy, with long-term monitoring occurring at the same rate as if the patient had
27 remained on IM injections, therefore representing no additional cost of oral therapy over IM
28 therapy following the initial switch.
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40 Cost of Injection Administration: Currently, physicians, nurses, and pharmacists are authorized
41 to administer B₁₂ by intramuscular injection in Alberta. Fees for physician office administration of
42 injections and pharmacist administration of injections are provided in Table 1.
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49 Quantity of Injection Administrations: It is unknown the proportion of patients on IM B₁₂ therapy
50 receiving their monthly injections from their physician's office or their pharmacy. For the purpose
51 of the study, based on the experience of the authors including a practicing pharmacist and
52 family physician, it was assumed that 25% of all B₁₂ injections are administered in a community
53 pharmacy with the remainder administered in a medical clinic.
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5 Cost of Additional Physician Visits: The current cost for a standard family physician consultation
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7 visit in Alberta of \$35.91 was utilized in the model.
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11 Quantity of Additional Physician Visits: Based on available administrative data, we were unable
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13 to determine the number of additional physician visits received by and billed for patients on IM
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15 versus oral B₁₂ supplementation apart from simply the administration of the injection in the
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17 medical clinic. For the base case scenario, we assumed that 10% of injections administered in a
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19 physician's office also included a billed physician consultation which would not have occurred if
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21 the patient were not on IM B₁₂, and have explored other scenarios in sensitivity analyses as
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23 described below.
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29 **Model Assumptions:**

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32 A number of assumptions were made with the model in addition to those previously described. It
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34 was assumed that patients on oral B₁₂ therapy were able to self-administer the medication, and
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36 if assistance was required, it was assumed that they already required this assistance for other
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38 medications rather than solely for B₁₂ tablets. Since B₁₂ tablets can be taken concurrently with
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40 other medications, it was not assumed that additional assistance would be needed if oral B₁₂
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42 were added to their medication regimen. The cost of supplies to administer the intramuscular
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44 injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded
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46 from the model as these are relatively inexpensive and were not felt to significantly contribute to
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48 the overall cost of the injectable product.
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53 **Discounting:**

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Consistent with CADTH guidelines for the economic evaluation of health technologies [243], a discount rate of 5% for outcomes occurring after one year was applied to the reference case, with sensitivity analyses performed around this value as described below.

Sensitivity Analyses:

Multi-way sensitivity analysis was performed in the form of 10,000 Monte Carlo simulation iterations, adjusting for a number of variables. Model inputs and the probabilistic distributions used in the sensitivity analyses are presented in Table 1. The base case scenario was calculated using the expected value for each variable and assumed a 10% rate of additional physician consultations for patients on intramuscular versus oral therapy.

Table 1. Expected Values and Distribution Parameters for the Deterministic Model and Probabilistic Sensitivity Analyses

Parameter	Expected Value \pm SE	Distribution
Study population	28,252 \pm 10%	Gamma
Cost per B ₁₂ tablet	\$0.16 \pm 0.008	Gamma
Professional Fee for Dispensing Tablets [2019]	\$11.93	--
Cost per B ₁₂ injectable dose [2019-224]	\$0.75	--
Cost for CBC and serum B ₁₂ analyses*	\$6.50	--
Laboratory technician time for blood sample draw and analyses (hours)*	0.75 (range 0.25-1)	Triangular
Laboratory technician wage and benefits [232]*	\$44.60 (range \$35.82-\$51.41)	Triangular
Fee for administration of intramuscular injection in a physician's office [254]	\$10.30	--
Cost for physician consultation visit [254]	\$35.91	--
Fee for administration of intramuscular injection in a pharmacy [265]	\$20.00	--

- SE=Standard Error; CBC=Complete blood count
- * indicates parameter only included in year 1 of the model
- Normal distribution samples values probabilistically from a normal curve with specified mean (expected value) and standard error. Triangular distribution samples values probabilistically within the range specified, with increasing probability as values near the expected value.

Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office consultations during injection visits, the analyses were repeated for rates of 0% and 25%. Discounting rates of 0% and 3% were also tested in sensitivity analysis.

RESULTS:

Estimated five-year cost savings associated with switching all Alberta seniors currently receiving injectable B₁₂ to oral therapy is \$13,975,883. Base scenario and sensitivity analysis results are presented in Table 2. Our model found that even if no additional physician visits were billed for among patients receiving IM therapy, over \$8 million could be saved from reduced administration costs alone.

Table 2. Model Results Over 5 Years

Proportion In-Office Injections Including a Fee for a Physician Visit	Discounting Rate for Years 2-5	Mean Cost Saving For Payer	Mean Cost Saving per Patient
Reference Case			
10%	5%	\$13,975,883	\$494.69
Sensitivity Analyses			
0%	0%	\$9,564,224	\$338.53
0%	3%	\$8,878,728	\$314.27
0%	5%	\$8,444,346	\$298.89
10%	0%	\$15,677,500	\$554.92
10%	3%	\$14,635,912	\$518.05
25%	0%	\$24,784,224	\$877.26
25%	3%	\$23,212,469	\$821.62
25%	5%	\$22,216,488	\$786.37

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3 Due to the additional laboratory monitoring performed in the year of the change from IM to oral
4 therapy, the model found the switch to be moderately cost-effective in the first year, with larger
5 savings realized in years 2-5. For the base scenario, cost savings in year 1 were estimated at
6 \$48.34 (SD \$8.58) per patient, increasing to \$126.55 (SD \$2.04) in year 2. Over 5 years,
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8 average cost-savings per patient was estimated at \$494.69.
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14 15 16 **DISCUSSION:** 17

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20 Over five years, the province of Alberta can be expected to free nearly \$14 million in healthcare
21 costs if all seniors over the age of 65 currently receiving IM B₁₂ are switched to oral tablets.
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24 Despite evidence confirming that sufficient B₁₂ is absorbed by passive diffusion at a dose of
25 1000 mcg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal
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27 disease [132], the intramuscular route continues to be commonly prescribed. With high health
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29 professional workloads and increasingly restricted healthcare budgets, a switch from IM to oral
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31 therapy will not only free health professional resources to see patients at greater need, but can
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33 also result in cost-savings for reinvestment into other needed services.
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40 The option of oral supplementation is well received by patients. A Canadian study by Kwong *et*
41
42 *al.* found that 73% of patients receiving B₁₂ injections were willing to try oral B₁₂, and of those
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44 who tried the oral therapy, 71% wished to permanently remain on oral therapy [7]. Travel
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46 inconveniences were the most common reason for preferring the oral route. The authors
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48 concluded that oral therapy would decrease physician burden, increase patient control over
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50 therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding
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52 injections is unknown in adult patients, previous research has suggested that patients with
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54 diabetes value a reduced injection burden as much as they value disease control [276].
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58 Therefore, if a societal perspective including utility were considered, it is likely that the benefit of
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3 switching patients from IM to oral therapy would be even greater. Furthermore, the elimination
4 of risk for injection site reactions following a switch to oral therapy represents another potential
5 benefit from the patient perspective.
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11 A number of assumptions employed in the model have the potential to alter the results in either
12 direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy
13 rather than monthly refills, which would be expected to underestimate the cost-saving potential
14 of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have
15 also occurred as a result of calculating tablet cost based on non-generic products at higher
16 costs per tablet. Home care costs for the administration of B₁₂ injections in home-bound patients
17 was not included since the proportion of patients receiving in-home injections was unknown,
18 and it was assumed that these injections would be administered in conjunction with a regular
19 visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits
20 are indeed being performed for B₁₂ injections, then the savings of switching to oral B₁₂ would
21 obviously be greater. Importantly, the model also assumed that all patients making the switch to
22 oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore
23 representing maximum saving potential. This assumption is consistent with previously published
24 randomized controlled trials and case series reporting treatment success across all patients
25 studied [2-87]. Additionally, we assumed in the base scenario that additional laboratory
26 monitoring is only required for the first year following the switch to oral therapy, with monitoring
27 as usual for the remaining years. Considering that adherence to self-administered oral therapy
28 may be lower than a healthcare professional-administered injection, even if an additional set of
29 laboratory tests were performed each year for the 5-year term of the model, estimated cost
30 savings would still amount to \$12 million.
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3 Direct comparison between our model and the results of the 2001 cost-saving paper cannot be
4 performed due to differing model assumptions and available data. Overall, both models report
5 significant cost-saving potential of the switch from the perspective of a government payer over
6 five years. However, due to higher current professional fees for injection administration, our
7 model found overall cost-savings even if no additional physician visits occurred for patients
8 receiving B₁₂ injections, whereas the previous study found a break-even point when 16.3% of
9 additional physician visits were avoided.
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21 The use of cost-minimization analysis is controversial as it assumes equal efficacy and
22 tolerability between the two options being compared; however, we feel this assumption is
23 justifiable based on published data comparing the oral and intramuscular routes [2-87].
24
25 However, the total number of patients studied in the randomized trials (total n=141 across 3
26 studies) and case series (n=15187) remains relatively small and doses employed across each
27 study differed. Further research on a larger population, comparing standard-dose IM therapy to
28 standard-dose oral therapy is therefore recommended and is currently being planned.
29
30 Additionally, payers considering adding oral B₁₂ tablets to their formularies should consider
31 allowing for the coverage of intramuscular therapy in the event of documented treatment failure
32 on oral supplementation, until larger-scale studies confirming equivalence are conducted, or
33 allowing for short-term IM therapy for patients with neurologic symptoms followed by oral
34 maintenance therapy. Indeed, a planned randomized controlled trial of 320 patients age ≥65 in
35 Spain will be directly comparing oral to IM B₁₂ and is expected to examine non-inferiority of oral
36 therapy over one year (clinicaltrials.gov NCT01476007).
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53 Overall, our model estimates that \$8-24 million in cost-savings can be realized over five years if
54 all Alberta seniors currently receiving IM vitamin B₁₂ are switched to oral therapy. Within closed
55 systems like universal healthcare, this is unlikely to represent true cost savings, but rather room
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3 for re-allocation of resources to other health system needs. With an aging population and
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5 increasing rates of chronic disease, switching of patients from IM to oral vitamin B₁₂
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7 replacement appears to be not only clinically efficacious, but also an effective use of limited
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9 healthcare resources.
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17
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27 REFERENCES

- 28
29
30
31 1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. JAMA
32
33 1991;**265**:94-5.
34
35 2. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of
36
37 cobalamin deficiency with oral cobalamin. Blood 1998;**92**(4):1191-1198.
38
39 3. Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. Oral versus
40
41 intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective,
42
43 randomized, open-label study. Clin Ther 2003;**25**(12):3124-3134.
44
45 4. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, et al. Comparing the
46
47 Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent
48
49 Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-
50
51 Label, Parallel-Group Study. Clin Ther 2011;**33**(3):358-71.
52
53 5. Nyholm E, Turpin P, Swain D, Cunningham B, Daly S, Nightingale P, et al. Oral vitamin B12
54
55 can change our practice. Postgrad Med J 2003;**79**:218-220.
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46
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56
57
58
59
60
6. Vidal-Alaball J, Butler C, Cannings-John R, Goringe A, Hood K, McCaddon A, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD004655. DOI:10.1002/14651858.CD004655.pub2.
 7. Kwong JC, Carr D, Dhalla IA, Tom-Kun D, Upshur REG. Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. *BMC Fam Pract* 2005;**6**:8.
 8. [Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. *Acta Med Scand* 1968;**184**:247-58.](#)
 - ~~8~~.9. Graham ID, Jette N, Tetroe J, Robinson N, Milne S, Mitchell SL. Oral cobalamin remains medicine's best kept secret. *Archives of Gerontology and Geriatrics* 2007;**44**(1):49–59.
 - ~~9~~.10. MacFarlane AJ, Greene-Finestone LS, Shi Y. Vitamin B-12 and homocysteine status in a folate-replete population: results from the Canadian Health Measures Survey. *Am J Clin Nutr* 2011;**94**:1079-87.
 - ~~10~~.11. Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;**60**:2-11.
 - ~~11~~.12. de Jager J, Kooy A, Lehert P, Wulffele MG, van der Kolk J, Bets D, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomized placebo controlled trial. *Br Med J* 2010;**340**:c2181.
 - ~~12~~.13. Andrès E, Vidal-Alaball J, Federici L, Henoun Loukili N, Zimmer J, Kaltenbach G. Clinical aspects of cobalamin deficiency in elderly patients. Epidemiology, causes, clinical manifestations, and treatment with special focus on oral cobalamin therapy. *Eur J Int Med* 2007;**18**:456-62.
 - ~~13~~.14. Andrès E, Federici L, Affenberger S, Vidal-Alaball J, Henoun Loukili N, et al. B12 deficiency: A look beyond pernicious anemia. *J Fam Pract* 2007;**56**(7):537-42.

- 1
2
3 | 14-15. Health Canada. Dietary Reference Intakes: Reference Values for Vitamins. Accessed 17
4 | May 2012 at <http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref_vitam_tbl-eng.php>.
5
6
7 | 15-16. van Walraven CG, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements:
8 | How much money could be saved by switching from injections to pills? Can Med Assoc J
9 | 2001;**47**:79-86.
10
11
12 | 16-17. Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district
13 | nurse. BMJ 1985;**270**:1254-1255.
14
15
16 | 17-18. Drummond MF, Sculpher MJ, Torrance G, O'Brien B, Stoddart G. Methods for the
17 | Economic Evaluation of Health Care Programmes. 3rd ed. New York: Oxford University
18 | Press; 2005.
19
20
21 | 18-19. IMS Brogan LRx database, January 2013 and Compuscript audit, January 2013.
22
23 | 19-20. Alberta Health. Pharmacy fee reimbursement. Retrieved from:
24 | <http://www.health.alberta.ca/services/pharmacy-fee-reimbursement.html>
25
26
27 | 20-21. Alberta Health. Coverage for Seniors. Retrieved from:
28 | <http://www.health.alberta.ca/services/drugs-seniors.html>
29
30
31 | 21-22. Alberta Health. Interactive Drug Benefit List. Retrieved from:
32 | <https://idbl.ab.bluecross.ca/idbl/load.do>
33
34
35 | 22-23. Government of Alberta. 2011 Alberta Wage and Salary Data – Medical Laboratory
36 | Technologist. Retrieved from:
37 | http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140
38
39
40 | 23-24. *Guidelines for the economic evaluation of health technologies: Canada* [3rd Edition].
41 | Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
42
43
44 | 24-25. Alberta Health Care Insurance Plan. Medical Price List as of 01 April 2012. Retrieved
45 | from: <http://www.health.alberta.ca/documents/SOMB-Medical-Prices-2012-04.pdf>
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43
44
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46
47
48
49
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59
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~~25-26.~~ Alberta Health. Compensation for Pharmacy Services, July 2012. Retrieved from:
<http://www.health.alberta.ca/documents/Pharmacy-Services-Compensation-2012.pdf>

~~26-27.~~ Hauber AB, Johnson FR, Sauriol L, Lescauwat B. Risking health to avoid injections:
Preferences of Canadians with type 2 diabetes. Diabetes Care 2005;28(9):2243-5.

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EVEREST Statement

	Study section	Additional remarks
Study design		
(1) The research question is stated	Background	
(2) The economic importance of the research question is stated	Background	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods (Study Type); Discussion	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Background; Methods	
(5) The alternatives being compared are clearly described	Methods (Cost Determination)	
(6) The form of economic evaluation used is stated	Methods (Study Type)	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Methods; Discussion	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods (Study Type)	
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A (based on multiple studies)	3 randomized controlled trials and 2 prospective case series
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods (Primary Outcome)	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	Methods (Setting/Patients)	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods (Cost Determination)	
(17) Methods for the estimation of quantities and unit costs are described	Methods (Cost Determination)	
(18) Currency and price data are recorded	Methods (Primary Outcome)	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	

(20) Details of any model used are given	Methods (Model Assumptions, Discounting, Sensitivity Analyses)	
(21) The choice of model used and the key parameters on which it is based are justified	Methods (Study Type); Discussion	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods (Study Type)	
(23) The discount rate(s) is stated	Methods (Discounting)	
(24) The choice of rate(s) is justified	Methods (Discounting)	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods (Sensitivity Analyses)	
(28) The choice of variables for sensitivity analysis is justified	Methods (Sensitivity Analyses)	
(29) The ranges over which the variables are varied are stated	Table 1	
(30) Relevant alternatives are compared	Introduction	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	N/A	
(33) The answer to the study question is given	Results; Discussion	
(34) Conclusions follow from the data reported	Discussion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	



Should Vitamin B12 Tablets be Included in More Canadian Drug Formularies? An Economic Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular Vitamin B12 Maintenance Therapy for Alberta Seniors

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3 Should Vitamin B₁₂ Tablets be Included in More Canadian Drug Formularies? An Economic
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5 Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular
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7 Vitamin B₁₂ Maintenance Therapy for Alberta Seniors
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49 **Keywords:** Cost analysis, healthcare costs, vitamin B₁₂ deficiency
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53 **Word Count:** 2911
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ABSTRACT:

Objectives: The aim of this study is to estimate the cost-savings attainable if all patients aged ≥ 65 in Alberta, Canada, currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

Setting: Primary care setting in Alberta, Canada.

Participants: Seniors age 65 and older currently receiving intramuscular vitamin B₁₂ therapy.

Intervention: Oral vitamin B₁₂ therapy at 1000 mcg per day versus intramuscular therapy at 1000 mcg per month.

Primary and Secondary Outcome Measures: Cost-saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring, and physician visit fees.

Results: Over 5 years, if all Albertans age 65 and older who currently receive intramuscular B₁₂ are switched to oral therapy, our model found that CAD \$13,975,883 can be saved. Even if no additional physician visits are billed for among patients receiving IM therapy, \$8,444,346 could be saved from reduced administration costs alone.

Conclusions: Oral B₁₂ therapy has been shown to be an effective therapeutic option for patients with vitamin B₁₂ deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation.

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3 To ensure judicious use of limited health resources, clinicians and formulary committees are
4 encouraged to adopt oral B₁₂ therapy as a clinically- and cost-effective first line therapy for
5 vitamin B₁₂ deficiency.
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10 11 **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

- 14 • Minimal assumptions built into the model, as exact costs and the exact number of
15 eligible residents comprising the population were available
- 16
17 • Three randomized controlled trials and two prospective case series support our use of a
18 cost-minimization analysis approach
- 19
20 • Comprehensive sensitivity analyses employed using Monte Carlo simulation to
21 incorporate multiple variables
- 22
23 • Study is from the perspective of the provincial ministry of health (the payer) and does not
24 adopt a societal perspective since much of the additional information required for that is
25 not available
- 26
27 • Despite being set in one Canadian province, the use of intramuscular B₁₂ therapy is
28 prevalent worldwide. Therefore, these results, while not directly generalizable to other
29 jurisdictions, point to an economic argument for greater uptake of oral B₁₂ therapy which
30 is likely consistent across other jurisdictions
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45 **BACKGROUND:**

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48 For over twenty years, oral vitamin B₁₂ has been referred to as “medicine’s best kept secret” [1].
49 Hesitation by clinicians to treat B₁₂ deficiency with oral preparations dates back to a 1959 report
50 by the U.S.P. Anti-Anemia Preparations Advisory Board suggesting inadequate absorption of
51 oral dosage forms. [2] Despite evidence of the effectiveness of oral B₁₂ therapy since [3-9],
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3 intramuscular (IM) administration remains the most commonly prescribed route in North
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5 America [10].
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10 Approximately 5% of Canadians are B₁₂ deficient [11], with Framingham data suggesting that
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12 B₁₂ deficiency in community-dwelling adults age 67 and older may be as high as 12% [12].
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14 Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use
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16 of antacids and other medications (metformin), inadequate animal product intake, and a
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18 deficiency in intrinsic factor required for the absorption of cobalamin from the gut [13-14]. While
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20 the absorbability of oral B₁₂ has been questioned, a number of studies have reported successful
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22 results with oral therapy including treatment in patients with pernicious anemia or bowel
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24 resection [5, 6, 9, 15]. Since 1% of orally-ingested B₁₂ is absorbed via passive diffusion
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26 independent of the presence of intrinsic factor [8], daily oral doses of 1000 mcg or more are
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28 considered sufficient to meet daily requirements [16] even in patients with insufficient intrinsic
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30 factor.
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35 While oral tablets often cost more to acquire than B₁₂ injection solution, the costs associated
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37 with administering the injections in the form of health professionals' time and resources can be
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39 significant. A 2001 cost study estimated that between \$2.9-17.6 million could be saved over 5
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41 years in the province of Ontario if elderly patients on IM B₁₂ were switched to oral therapy [17].
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43 In addition, a British study estimated that 2000 nursing hours are required to provide one year of
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45 injections to 492 patients in their homes [18]. Across Canada, only Nova Scotia, Northwest
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47 Territories, Yukon, and the Non-Insured Health Benefits program for First Nations and Inuit
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49 consider oral B₁₂ tablets to be a benefit in their provincial drug formularies, while all provinces
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51 and territories cover the injectable product.
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3 The objective of this study is to estimate the cost savings of treatment using daily oral vitamin
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5 B₁₂ supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular
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7 injections in Alberta seniors over the age of 65 who are currently using B₁₂ injection. Such a
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9 study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to
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11 renew discussion about the best allocation of limited healthcare resources and whether oral B₁₂
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13 should be covered by all Canadian provincial formularies.
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18 **METHODS:**

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22 **Study Type:** A cost-minimization analysis (CMA) was performed wherein alternatives compared
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24 are considered to be equivalent in terms of factors that are relevant to the decision such as
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26 efficacy and tolerability, so the lowest cost alternative is selected [19]. While a major
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28 assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75
29
30 patients on IM therapy) [3-5] and three prospective case series of 151 patients switching from
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32 IM to oral therapy [6, 8, 9] have concluded that the oral route is as clinically effective as the
33
34 intramuscular route. Across all case series, no patients switched from IM to oral therapy
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36 required a switch back to IM replacement as a result of therapeutic failure. Costs were modeled
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38 over a period of five years, and the perspective of the Alberta Ministry of Health was adopted for
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40 this study.
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47 **Setting / Patients:** The study population consists of individuals aged 65 or older with an Alberta
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49 Health Care number receiving IM B₁₂ therapy. The number of Alberta seniors dispensed
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51 injectable B₁₂ over a 1-year period (January-December 2012) was determined from prescription
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53 dispensing records collected by IMS Brogan [20].
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3 **Primary Outcome:** Cost-savings achievable by the province of Alberta if patients aged ≥ 65 and
4 currently receiving IM B₁₂ therapy are switched to oral therapy. Cost savings are estimated in
5 Canadian currency.
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11 **Cost Determination:**

12 All costs are reported in Canadian dollars.
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18 Cost of B₁₂ Tablets: The suggested retail price of Swiss Naturals[®], Jamieson[®], and Nature's
19 Bounty[®] brands of 1000 mcg B₁₂ tablets were obtained from the manufacturers and averaged to
20 obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing
21 products with an acquisition cost of $\leq \$74.99$ is \$11.93 (consists of \$10.22 professional fee and
22 \$1.71 inventory allowance) [21].
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31 Quantity of B₁₂ Tablets and Professional Fees: It was assumed that patients would receive a
32 three-month supply with each fill, therefore amassing four professional fees annually and 365
33 tablets. Albertans age 65 and older are automatically enrolled into a 'Coverage for Seniors'
34 program, where the patient co-pay is 30% of the cost to a maximum of \$25 [22]. Since this study
35 assumes the perspective of the provincial Ministry of Health, the payer is assumed to cover 70%
36 of the total drug cost. Despite being a non-prescription product, sales tax was not applied since
37 such tablets would be dispensed through the pharmacy as a tax-free product similar to a
38 prescription drug.
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51 Cost of B₁₂ Injection: Parenteral B₁₂ in Alberta is available in 10 mL multi-dose vials at a
52 concentration of 1000 mcg/mL. The cost per mL for the two products currently available in
53 Alberta (DIN 00521515 and DIN 01987003) were determined from the Alberta Health Drug
54 Benefit List [23]. In Alberta, the total charge allowable for injectable drugs other than insulin is
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3 5/3 of the product's acquisition cost [21]. Therefore, with an acquisition cost of \$4.50 per vial of
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5/3 of the product's acquisition cost [21]. Therefore, with an acquisition cost of \$4.50 per vial of parenteral B₁₂, the total charge allowed – including the drug and professional fee – cannot exceed \$7.50, or \$0.75 per dose.

Quantity of B₁₂ injection: At the usual dosage of 1000 mcg/month, one vial contains a ten-month supply of drug. Therefore, 1.2 vials would be required for a one-year supply.

Cost of Additional Laboratory Monitoring: Costs for the laboratory analyses were obtained from Alberta Health Services, laboratory technicians' time to draw and analyze the blood samples were estimated by consulting with practicing laboratory technicians, and laboratory technician wages were obtained from a Government of Alberta occupational survey [24] with a 20% fringe benefit applied.

Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we assumed that patients to be switched from IM to oral B₁₂ would receive a baseline complete blood count and serum B₁₂ prior to the switch, repeated once after the switch to confirm effectiveness. It was assumed that this additional monitoring would occur only upon switch from IM to oral therapy, with long-term monitoring occurring at the same rate as if the patient had remained on IM injections, therefore representing no additional cost of oral therapy over IM therapy following the initial switch.

Cost of Injection Administration: Currently, physicians, nurses, and pharmacists are authorized to administer B₁₂ by intramuscular injection in Alberta. Fees for physician office administration of injections and pharmacist administration of injections are provided in Table 1.

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3 Quantity of Injection Administrations: It is unknown the proportion of patients on IM B₁₂ therapy
4 receiving their monthly injections from their physician's office or their pharmacy. For the purpose
5 of the study, based on the experience of the authors including a practicing pharmacist and
6 family physician, it was assumed that 25% of all B₁₂ injections are administered in a community
7 pharmacy with the remainder administered in a medical clinic.
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16 Cost of Additional Physician Visits: The current cost for a standard family physician consultation
17 visit in Alberta of \$35.91 was utilized in the model.
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23 Quantity of Additional Physician Visits: Based on available administrative data, we were unable
24 to determine the number of additional physician visits received by and billed for patients on IM
25 versus oral B₁₂ supplementation apart from simply the administration of the injection in the
26 medical clinic. For the base case scenario, we assumed that 10% of injections administered in a
27 physician's office also included a billed physician consultation which would not have occurred if
28 the patient were not on IM B₁₂, and have explored other scenarios in sensitivity analyses as
29 described below.
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40 **Model Assumptions:**

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43 A number of assumptions were made with the model in addition to those previously described. It
44 was assumed that patients on oral B₁₂ therapy were able to self-administer the medication, and
45 if assistance was required, it was assumed that they already required this assistance for other
46 medications rather than solely for B₁₂ tablets. Since B₁₂ tablets can be taken concurrently with
47 other medications, it was not assumed that additional assistance would be needed if oral B₁₂
48 were added to their medication regimen. The cost of supplies to administer the intramuscular
49 injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded
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from the model as these are relatively inexpensive and were not felt to significantly contribute to the overall cost of the injectable product.

Discounting:

Consistent with CADTH guidelines for the economic evaluation of health technologies [24], a discount rate of 5% for outcomes occurring after one year was applied to the reference case, with sensitivity analyses performed around this value as described below.

Sensitivity Analyses:

Multi-way sensitivity analysis was performed in the form of 10,000 Monte Carlo simulation iterations, adjusting for a number of variables. Model inputs and the probabilistic distributions used in the sensitivity analyses are presented in Table 1. The base case scenario was calculated using the expected value for each variable and assumed a 10% rate of additional physician consultations for patients on intramuscular versus oral therapy.

Table 1. Expected Values and Distribution Parameters for the Deterministic Model and Probabilistic Sensitivity Analyses

Parameter	Expected Value \pm SE	Distribution
Study population	28,252 \pm 10%	Gamma
Cost per B ₁₂ tablet	\$0.16 \pm 0.008	Gamma
Professional Fee for Dispensing Tablets [20]	\$11.93	--
Cost per B ₁₂ injectable dose [20-22]	\$0.75	--
Cost for CBC and serum B ₁₂ analyses*	\$6.50	--
Laboratory technician time for blood sample draw and analyses (hours)*	0.75 (range 0.25-1)	Triangular
Laboratory technician wage and benefits [23]*	\$44.60 (range \$35.82-\$51.41)	Triangular
Fee for administration of intramuscular injection in a physician's office [25]	\$10.30	--

Cost for physician consultation visit [25]	\$35.91	--
Fee for administration of intramuscular injection in a pharmacy [26]	\$20.00	--

- SE=Standard Error; CBC=Complete blood count
- * indicates parameter only included in year 1 of the model
- Normal distribution samples values probabilistically from a normal curve with specified mean (expected value) and standard error. Triangular distribution samples values probabilistically within the range specified, with increasing probability as values near the expected value.

Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office consultations during injection visits, the analyses were repeated for rates of 0% and 25%. Discounting rates of 0% and 3% were also tested in sensitivity analysis.

RESULTS:

Estimated five-year cost savings associated with switching all Alberta seniors currently receiving injectable B₁₂ to oral therapy is \$13,975,883. Base scenario and sensitivity analysis results are presented in Table 2. Our model found that even if no additional physician visits were billed for among patients receiving IM therapy, over \$8 million could be saved from reduced administration costs alone.

Table 2. Model Results Over 5 Years

Proportion In-Office Injections Including a Fee for a Physician Visit	Discounting Rate for Years 2-5	Mean Cost Saving For Payer	Mean Cost Saving per Patient
Reference Case			
10%	5%	\$13,975,883	\$494.69
Sensitivity Analyses			
0%	0%	\$9,564,224	\$338.53
0%	3%	\$8,878,728	\$314.27

0%	5%	\$8,444,346	\$298.89
10%	0%	\$15,677,500	\$554.92
10%	3%	\$14,635,912	\$518.05
25%	0%	\$24,784,224	\$877.26
25%	3%	\$23,212,469	\$821.62
25%	5%	\$22,216,488	\$786.37

Due to the additional laboratory monitoring performed in the year of the change from IM to oral therapy, the model found the switch to be moderately cost-effective in the first year, with larger savings realized in years 2-5. For the base scenario, cost savings in year 1 were estimated at \$48.34 (SD \$8.58) per patient, increasing to \$126.55 (SD \$2.04) in year 2. Over 5 years, average cost-savings per patient was estimated at \$494.69.

DISCUSSION:

Over five years, the province of Alberta can be expected to free nearly \$14 million in healthcare costs if all seniors over the age of 65 currently receiving IM B₁₂ are switched to oral tablets. Despite evidence confirming that sufficient B₁₂ is absorbed by passive diffusion at a dose of 1000 mcg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal disease [14], the intramuscular route continues to be commonly prescribed. With high health professional workloads and increasingly restricted healthcare budgets, a switch from IM to oral therapy will not only free health professional resources to see patients at greater need, but can also result in cost-savings for reinvestment into other needed services.

The option of oral supplementation is well received by patients. A Canadian study by Kwong *et al.* found that 73% of patients receiving B₁₂ injections were willing to try oral B₁₂, and of those who tried the oral therapy, 71% wished to permanently remain on oral therapy [8]. Travel

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3 inconveniences were the most common reason for preferring the oral route. The authors
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5 concluded that oral therapy would decrease physician burden, increase patient control over
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7 therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding
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9 injections is unknown in adult patients, previous research has suggested that patients with
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11 diabetes value a reduced injection burden as much as they value disease control [28].
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14 Therefore, if a societal perspective including utility were considered, it is likely that the benefit of
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16 switching patients from IM to oral therapy would be even greater. Furthermore, the elimination
17
18 of risk for injection site reactions following a switch to oral therapy represents another potential
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20 benefit from the patient perspective.
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25 A number of assumptions employed in the model have the potential to alter the results in either
26
27 direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy
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29 rather than monthly refills, which would be expected to underestimate the cost-saving potential
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31 of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have
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33 also occurred as a result of calculating tablet cost based on non-generic products at higher
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35 costs per tablet. Home care costs for the administration of B₁₂ injections in home-bound patients
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37 was not included since the proportion of patients receiving in-home injections was unknown,
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39 and it was assumed that these injections would be administered in conjunction with a regular
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41 visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits
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43 are indeed being performed for B₁₂ injections, then the savings of switching to oral B₁₂ would
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45 obviously be greater. Importantly, the model also assumed that all patients making the switch to
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47 oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore
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49 representing maximum saving potential. This assumption is consistent with previously published
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51 randomized controlled trials and case series reporting treatment success across all patients
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53 studied [3-9]. Additionally, we assumed in the base scenario that additional laboratory
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55 monitoring is only required for the first year following the switch to oral therapy, with monitoring
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3 as usual for the remaining years. Considering that adherence to self-administered oral therapy
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5 may be lower than a healthcare professional-administered injection, even if an additional set of
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7 laboratory tests were performed each year for the 5-year term of the model, estimated cost
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9 savings would still amount to \$12 million.
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14 Direct comparison between our model and the results of the 2001 cost-saving paper cannot be
15
16 performed due to differing model assumptions and available data. Overall, both models report
17
18 significant cost-saving potential of the switch from the perspective of a government payer over
19
20 five years. However, due to higher current professional fees for injection administration, our
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22 model found overall cost-savings even if no additional physician visits occurred for patients
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24 receiving B₁₂ injections, whereas the previous study found a break-even point when 16.3% of
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26 additional physician visits were avoided.
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31 The use of cost-minimization analysis is controversial as it assumes equal efficacy and
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33 tolerability between the two options being compared; however, we feel this assumption is
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35 justifiable based on published data comparing the oral and intramuscular routes [3-9]. However,
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37 the total number of patients studied in the randomized trials (total n=141 across 3 studies) and
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39 case series (n=151) remains relatively small and doses employed across each study differed.
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41 Further research on a larger population, comparing standard-dose IM therapy to standard-dose
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43 oral therapy is therefore recommended and is currently being planned. Additionally, payers
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45 considering adding oral B₁₂ tablets to their formularies should consider allowing for the coverage
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47 of intramuscular therapy in the event of documented treatment failure on oral supplementation,
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49 until larger-scale studies confirming equivalence are conducted, or allowing for short-term IM
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51 therapy for patients with neurologic symptoms followed by oral maintenance therapy. Indeed, a
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53 planned randomized controlled trial of 320 patients age ≥65 in Spain will be directly comparing
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3 oral to IM B₁₂ and is expected to examine non-inferiority of oral therapy over one year
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5 (clinicaltrials.gov NCT01476007).
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10 Overall, our model estimates that \$8-24 million in cost-savings can be realized over five years if
11 all Alberta seniors currently receiving IM vitamin B₁₂ are switched to oral therapy. Within closed
12 systems like universal healthcare, this is unlikely to represent true cost savings, but rather room
13 for re-allocation of resources to other health system needs. With an aging population and
14 increasing rates of chronic disease, switching of patients from IM to oral vitamin B₁₂
15 replacement appears to be not only clinically efficacious, but also an effective use of limited
16 healthcare resources.
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10

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13 the design and analysis/interpretation of data, drafting of the article, and approval of the final
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15 version.
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17 **Competing Interests:** The authors declare no conflicts of interest related to the above work.
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20 **Data Sharing Statement:** There is no additional unpublished data related to this study.
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REFERENCES

1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. J Am Med Assoc 1991;**265**:94-5.
2. Bethell FH, Castle WB, Conley CL. Present status of treatment of pernicious anemia: Ninth announcement of the U.S.P. Anti-Anemia Preparations Advisory Board. J Am Med Assoc 1959;171(15):2092-4.
3. Kuzminski AM, Del Giacco EJ, Allen RH, et al. Effective treatment of cobalamin deficiency with oral cobalamin. Blood 1998;**92**(4):1191-1198.
4. Bolaman Z, Kadikoylu G, Yukselen V, et al. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective, randomized, open-label study. Clin Ther 2003;**25**(12):3124-3134.
5. Castelli MC, Friedman K, Sherry J, et al. Comparing the Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-Label, Parallel-Group Study. Clin Ther 2011;**33**(3):358-71.
6. Nyholm E, Turpin P, Swain D, et al. Oral vitamin B12 can change our practice. Postgrad Med J 2003;**79**:218-220.
7. Vidal-Alaball J, Butler C, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD004655. DOI:10.1002/14651858.CD004655.pub2.
8. Kwong JC, Carr D, Dhalla IA, et al. Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. BMC Fam Pract 2005;**6**:8.
9. Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. Acta Med Scand 1968;**184**:247-58.

- 1
2
3 10. Graham ID, Jette N, Tetroe J, et al. Oral cobalamin remains medicine's best kept secret.
4
5 Archives of Gerontology and Geriatrics 2007;**44**(1):49–59.
6
- 7
8 11. MacFarlane AJ, Greene-Finestone LS, Shi Y. Vitamin B-12 and homocysteine status in a
9
10 folate-replete population: results from the Canadian Health Measures Survey. Am J Clin
11
12 Nutr 2011;**94**:1079-87.
13
- 14
15 12. Lindenbaum J, Rosenberg IH, Wilson PW, et al. Prevalence of cobalamin deficiency in the
16
17 Framingham elderly population. Am J Clin Nutr 1994;**60**:2-11.
18
- 19
20 13. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type
21
22 2 diabetes and risk of vitamin B-12 deficiency: randomized placebo controlled trial. Br Med J
23
24 2010;**340**:c2181.
25
- 26
27 14. Andrès E, Vidal-Alaball J, Federici L, et al. Clinical aspects of cobalamin deficiency in elderly
28
29 patients. Epidemiology, causes, clinical manifestations, and treatment with special focus on
30
31 oral cobalamin therapy. Eur J Int Med 2007;**18**:456-62.
32
- 33
34 15. Andrès E, Federici L, Affenberger S, et al. B12 deficiency: A look beyond pernicious anemia.
35
36 J Fam Pract 2007;**56**(7):537-42.
37
- 38
39 16. Health Canada. Dietary Reference Intakes: Reference Values for Vitamins. Accessed 17
40
41 May 2012 at <http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref_vitam_tbl-eng.php>.
42
- 43
44 17. van Walraven CG, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements:
45
46 How much money could be saved by switching from injections to pills? Can Med Assoc J
47
48 2001;**47**:79-86.
49
- 50
51 18. Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district
52
53 nurse. BMJ 1985;**270**:1254-1255.
54
- 55
56 19. Drummond MF, Sculpher MJ, Torrance G, et al. Methods for the Economic Evaluation of
57
58 Health Care Programmes. 3rd ed. New York: Oxford University Press; 2005.
59
- 60
60 20. IMS Brogan LRx database, January 2013 and Compuscript audit, January 2013.

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21. Alberta Health. Pharmacy fee reimbursement. Retrieved from:
<http://www.health.alberta.ca/services/pharmacy-fee-reimbursement.html>
 22. Alberta Health. Coverage for Seniors. Retrieved from:
<http://www.health.alberta.ca/services/drugs-seniors.html>
 23. Alberta Health. Interactive Drug Benefit List. Retrieved from:
<https://idbl.ab.bluecross.ca/idbl/load.do>
 24. Government of Alberta. 2011 Alberta Wage and Salary Data – Medical Laboratory Technologist. Retrieved from:
http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140
 25. *Guidelines for the economic evaluation of health technologies: Canada* [3rd Edition]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
 26. Alberta Health Care Insurance Plan. Medical Price List as of 01 April 2012. Retrieved from:
<http://www.health.alberta.ca/documents/SOMB-Medical-Prices-2012-04.pdf>
 27. Alberta Health. Compensation for Pharmacy Services, July 2012. Retrieved from:
<http://www.health.alberta.ca/documents/Pharmacy-Services-Compensation-2012.pdf>
 28. Hauber AB, Johnson FR, Sauriol L, et al. Risking health to avoid injections: Preferences of Canadians with type 2 diabetes. *Diabetes Care* 2005;28(9):2243-5.

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3 Should Vitamin B₁₂ Tablets be Included in More Canadian Drug Formularies? An Economic
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5 Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular
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7 Vitamin B₁₂ Maintenance Therapy for Alberta Seniors
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ABSTRACT:

Objectives: The aim of this study is to estimate the cost-savings attainable if all patients aged ≥ 65 in Alberta, Canada, currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

Setting: Primary care setting in Alberta, Canada.

Participants: Seniors age 65 and older currently receiving intramuscular vitamin B₁₂ therapy.

Intervention: Oral vitamin B₁₂ therapy at 1000 mcg per day versus intramuscular therapy at 1000 mcg per month.

Primary and Secondary Outcome Measures: Cost-saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring, and physician visit fees.

Results: Over 5 years, if all Albertans age 65 and older who currently receive intramuscular B₁₂ are switched to oral therapy, our model found that CAD \$13,975,883 can be saved. Even if no additional physician visits are billed for among patients receiving IM therapy, \$8,444,346 could be saved from reduced administration costs alone.

Conclusions: Oral B₁₂ therapy has been shown to be an effective therapeutic option for patients with vitamin B₁₂ deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation.

To ensure judicious use of limited health resources, clinicians and formulary committees are encouraged to adopt oral B₁₂ therapy as a clinically- and cost-effective first line therapy for vitamin B₁₂ deficiency.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- Minimal assumptions built into the model, as exact costs and the exact number of eligible residents comprising the population were available
- Three randomized controlled trials and two prospective case series support our use of a cost-minimization analysis approach
- Comprehensive sensitivity analyses employed using Monte Carlo simulation to incorporate multiple variables
- Study is from the perspective of the provincial ministry of health (the payer) and does not adopt a societal perspective since much of the additional information required for that is not available
- Despite being set in one Canadian province, the use of intramuscular B₁₂ therapy is prevalent worldwide. Therefore, these results, while not directly generalizable to other jurisdictions, point to an economic argument for greater uptake of oral B₁₂ therapy which is likely consistent across other jurisdictions

BACKGROUND:

For over twenty years, oral vitamin B₁₂ has been referred to as “medicine’s best kept secret” [1].

[Hesitation by clinicians to treat B₁₂ deficiency with oral preparations dates back to a 1959 report by the U.S.P. Anti-Anemia Preparations Advisory Board suggesting inadequate absorption of oral dosage forms. \[2\]](#) Despite evidence of the effectiveness of oral B₁₂ therapy [since \[32-98\]](#),

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3 intramuscular (IM) administration remains the most commonly prescribed route in North
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5 America [109].
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10 Approximately 5% of Canadians are B₁₂ deficient [110], with Framingham data suggesting that
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12 B₁₂ deficiency in community-dwelling adults age 67 and older may be as high as 12% [124].
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14 Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use
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16 of antacids and other medications (metformin), inadequate animal product intake, and a
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18 deficiency in intrinsic factor required for the absorption of cobalamin from the gut [132-143].
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20 While the absorbability of oral B₁₂ has been questioned, a number of studies have reported
21
22 successful results with oral therapy including treatment in patients with pernicious anemia or
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24 bowel resection [54, 65, 98, 154]. Since 1% of orally-ingested B₁₂ is absorbed via passive
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26 diffusion independent of the presence of intrinsic factor [87], daily oral doses of 1000 mcg or
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28 more are considered sufficient to meet daily requirements [165] even in patients with insufficient
29
30 intrinsic factor.
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35 While oral tablets often cost more to acquire than B₁₂ injection solution, the costs associated
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37 with administering the injections in the form of health professionals' time and resources can be
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39 significant. A 2001 cost study estimated that between \$2.9-17.6 million could be saved over 5
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41 years in the province of Ontario if elderly patients on IM B₁₂ were switched to oral therapy
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43 [4617]. In addition, a British study estimated that 2000 nursing hours are required to provide one
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45 year of injections to 492 patients in their homes [187]. Across Canada, only Nova Scotia,
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47 Northwest Territories, Yukon, and the Non-Insured Health Benefits program for First Nations
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49 and Inuit consider oral B₁₂ tablets to be a benefit in their provincial drug formularies, while all
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51 provinces and territories cover the injectable product.
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3 The objective of this study is to estimate the cost savings of treatment using daily oral vitamin
4 B₁₂ supplementation at a dosage of 1000 mcg daily versus monthly 1000 mcg/mL intramuscular
5 injections in Alberta seniors over the age of 65 who are currently using B₁₂ injection. Such a
6 study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to
7 renew discussion about the best allocation of limited healthcare resources and whether oral B₁₂
8 should be covered by all Canadian provincial formularies.
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18 **METHODS:**

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22 **Study Type:** A cost-minimization analysis (CMA) was performed wherein alternatives compared
23 are considered to be equivalent in terms of factors that are relevant to the decision such as
24 efficacy and tolerability, so the lowest cost alternative is selected [198]. While a major
25 assumption, three randomized trials (including a total of 66 subjects on oral therapy and 75
26 patients on IM therapy) [32-54] and three prospective case series of 151 patients switching from
27 IM to oral therapy [65, 87, 98] have concluded that the oral route is as clinically effective as the
28 intramuscular route. Across all case series, no patients switched from IM to oral therapy
29 required a switch back to IM replacement as a result of therapeutic failure. Costs were modeled
30 over a period of five years, and the perspective of the Alberta Ministry of Health was adopted for
31 this study.
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46 **Setting / Patients:** The study population consists of individuals aged 65 or older with an Alberta
47 Health Care number receiving IM B₁₂ therapy. The number of Alberta seniors dispensed
48 injectable B₁₂ over a 1-year period (January-December 2012) was determined from prescription
49 dispensing records collected by IMS Brogan [2019].
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3 **Primary Outcome:** Cost-savings achievable by the province of Alberta if patients aged ≥ 65 and
4 currently receiving IM B₁₂ therapy are switched to oral therapy. Cost savings are estimated in
5 Canadian currency.
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12 **Cost Determination:**

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14 All costs are reported in Canadian dollars.
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18 Cost of B₁₂ Tablets: The suggested retail price of Swiss Naturals[®], Jamieson[®], and Nature's
19 Bounty[®] brands of 1000 mcg B₁₂ tablets were obtained from the manufacturers and averaged to
20 obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing
21 products with an acquisition cost of $\leq \$74.99$ is \$11.93 (consists of \$10.22 professional fee and
22 \$1.71 inventory allowance) [219].
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31 Quantity of B₁₂ Tablets and Professional Fees: It was assumed that patients would receive a
32 three-month supply with each fill, therefore amassing four professional fees annually and 365
33 tablets. Albertans age 65 and older are automatically enrolled into a 'Coverage for Seniors'
34 program, where the patient co-pay is 30% of the cost to a maximum of \$25 [224]. Since this
35 study assumes the perspective of the provincial Ministry of Health, the payer is assumed to
36 cover 70% of the total drug cost. Despite being a non-prescription product, sales tax was not
37 applied since such tablets would be dispensed through the pharmacy as a tax-free product
38 similar to a prescription drug.
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50 Cost of B₁₂ Injection: Parenteral B₁₂ in Alberta is available in 10 mL multi-dose vials at a
51 concentration of 1000 mcg/mL. The cost per mL for the two products currently available in
52 Alberta (DIN 00521515 and DIN 01987003) were determined from the Alberta Health Drug
53 Benefit List [232]. In Alberta, the total charge allowable for injectable drugs other than insulin is
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3 | 5/3 of the product's acquisition cost [210]. Therefore, with an acquisition cost of \$4.50 per vial of
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5 | parenteral B₁₂, the total charge allowed – including the drug and professional fee – cannot
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7 | exceed \$7.50, or \$0.75 per dose.
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11 | Quantity of B₁₂ injection: At the usual dosage of 1000 mcg/month, one vial contains a ten-month
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13 | supply of drug. Therefore, 1.2 vials would be required for a one-year supply.
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17 | Cost of Additional Laboratory Monitoring: Costs for the laboratory analyses were obtained from
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19 | Alberta Health Services, laboratory technicians' time to draw and analyze the blood samples
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21 | were estimated by consulting with practicing laboratory technicians, and laboratory technician
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23 | wages were obtained from a Government of Alberta occupational survey [243] with a 20% fringe
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25 | benefit applied.
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31 | Quantity of Additional Laboratory Monitoring: To ensure adequate response to therapy, we
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33 | assumed that patients to be switched from IM to oral B₁₂ would receive a baseline complete
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35 | blood count and serum B₁₂ prior to the switch, repeated once after the switch to confirm
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37 | effectiveness. It was assumed that this additional monitoring would occur only upon switch from
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39 | IM to oral therapy, with long-term monitoring occurring at the same rate as if the patient had
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41 | remained on IM injections, therefore representing no additional cost of oral therapy over IM
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43 | therapy following the initial switch.
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47 | Cost of Injection Administration: Currently, physicians, nurses, and pharmacists are authorized
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49 | to administer B₁₂ by intramuscular injection in Alberta. Fees for physician office administration of
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51 | injections and pharmacist administration of injections are provided in Table 1.
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3 Quantity of Injection Administrations: It is unknown the proportion of patients on IM B₁₂ therapy
4 receiving their monthly injections from their physician's office or their pharmacy. For the purpose
5 of the study, based on the experience of the authors including a practicing pharmacist and
6 family physician, it was assumed that 25% of all B₁₂ injections are administered in a community
7 pharmacy with the remainder administered in a medical clinic.
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16 Cost of Additional Physician Visits: The current cost for a standard family physician consultation
17 visit in Alberta of \$35.91 was utilized in the model.
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23 Quantity of Additional Physician Visits: Based on available administrative data, we were unable
24 to determine the number of additional physician visits received by and billed for patients on IM
25 versus oral B₁₂ supplementation apart from simply the administration of the injection in the
26 medical clinic. For the base case scenario, we assumed that 10% of injections administered in a
27 physician's office also included a billed physician consultation which would not have occurred if
28 the patient were not on IM B₁₂, and have explored other scenarios in sensitivity analyses as
29 described below.
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40 **Model Assumptions:**

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43 A number of assumptions were made with the model in addition to those previously described. It
44 was assumed that patients on oral B₁₂ therapy were able to self-administer the medication, and
45 if assistance was required, it was assumed that they already required this assistance for other
46 medications rather than solely for B₁₂ tablets. Since B₁₂ tablets can be taken concurrently with
47 other medications, it was not assumed that additional assistance would be needed if oral B₁₂
48 were added to their medication regimen. The cost of supplies to administer the intramuscular
49 injection (needle, syringe, alcohol swab, gloves, bandage, and sharps disposal) were excluded
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from the model as these are relatively inexpensive and were not felt to significantly contribute to the overall cost of the injectable product.

Discounting:

Consistent with CADTH guidelines for the economic evaluation of health technologies [24], a discount rate of 5% for outcomes occurring after one year was applied to the reference case, with sensitivity analyses performed around this value as described below.

Sensitivity Analyses:

Multi-way sensitivity analysis was performed in the form of 10,000 Monte Carlo simulation iterations, adjusting for a number of variables. Model inputs and the probabilistic distributions used in the sensitivity analyses are presented in Table 1. The base case scenario was calculated using the expected value for each variable and assumed a 10% rate of additional physician consultations for patients on intramuscular versus oral therapy.

Table 1. Expected Values and Distribution Parameters for the Deterministic Model and Probabilistic Sensitivity Analyses

Parameter	Expected Value \pm SE	Distribution
Study population	28,252 \pm 10%	Gamma
Cost per B ₁₂ tablet	\$0.16 \pm 0.008	Gamma
Professional Fee for Dispensing Tablets [20]	\$11.93	--
Cost per B ₁₂ injectable dose [20-22]	\$0.75	--
Cost for CBC and serum B ₁₂ analyses*	\$6.50	--
Laboratory technician time for blood sample draw and analyses (hours)*	0.75 (range 0.25-1)	Triangular
Laboratory technician wage and benefits [23]*	\$44.60 (range \$35.82-\$51.41)	Triangular
Fee for administration of intramuscular injection in a physician's office [25]	\$10.30	--

Cost for physician consultation visit [25]	\$35.91	--
Fee for administration of intramuscular injection in a pharmacy [26]	\$20.00	--

- SE=Standard Error; CBC=Complete blood count
- * indicates parameter only included in year 1 of the model
- Normal distribution samples values probabilistically from a normal curve with specified mean (expected value) and standard error. Triangular distribution samples values probabilistically within the range specified, with increasing probability as values near the expected value.

Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office consultations during injection visits, the analyses were repeated for rates of 0% and 25%. Discounting rates of 0% and 3% were also tested in sensitivity analysis.

RESULTS:

Estimated five-year cost savings associated with switching all Alberta seniors currently receiving injectable B₁₂ to oral therapy is \$13,975,883. Base scenario and sensitivity analysis results are presented in Table 2. Our model found that even if no additional physician visits were billed for among patients receiving IM therapy, over \$8 million could be saved from reduced administration costs alone.

Table 2. Model Results Over 5 Years

Proportion In-Office Injections Including a Fee for a Physician Visit	Discounting Rate for Years 2-5	Mean Cost Saving For Payer	Mean Cost Saving per Patient
Reference Case			
10%	5%	\$13,975,883	\$494.69
Sensitivity Analyses			
0%	0%	\$9,564,224	\$338.53
0%	3%	\$8,878,728	\$314.27

0%	5%	\$8,444,346	\$298.89
10%	0%	\$15,677,500	\$554.92
10%	3%	\$14,635,912	\$518.05
25%	0%	\$24,784,224	\$877.26
25%	3%	\$23,212,469	\$821.62
25%	5%	\$22,216,488	\$786.37

Due to the additional laboratory monitoring performed in the year of the change from IM to oral therapy, the model found the switch to be moderately cost-effective in the first year, with larger savings realized in years 2-5. For the base scenario, cost savings in year 1 were estimated at \$48.34 (SD \$8.58) per patient, increasing to \$126.55 (SD \$2.04) in year 2. Over 5 years, average cost-savings per patient was estimated at \$494.69.

DISCUSSION:

Over five years, the province of Alberta can be expected to free nearly \$14 million in healthcare costs if all seniors over the age of 65 currently receiving IM B₁₂ are switched to oral tablets. Despite evidence confirming that sufficient B₁₂ is absorbed by passive diffusion at a dose of 1000 mcg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal disease [143], the intramuscular route continues to be commonly prescribed. With high health professional workloads and increasingly restricted healthcare budgets, a switch from IM to oral therapy will not only free health professional resources to see patients at greater need, but can also result in cost-savings for reinvestment into other needed services.

The option of oral supplementation is well received by patients. A Canadian study by Kwong *et al.* found that 73% of patients receiving B₁₂ injections were willing to try oral B₁₂, and of those who tried the oral therapy, 71% wished to permanently remain on oral therapy [87]. Travel

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3 inconveniences were the most common reason for preferring the oral route. The authors
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5 concluded that oral therapy would decrease physician burden, increase patient control over
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7 therapy, and avoid patient discomfort and inconvenience. While willingness-to-pay for avoiding
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9 injections is unknown in adult patients, previous research has suggested that patients with
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11 diabetes value a reduced injection burden as much as they value disease control [287].
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14 Therefore, if a societal perspective including utility were considered, it is likely that the benefit of
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16 switching patients from IM to oral therapy would be even greater. Furthermore, the elimination
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18 of risk for injection site reactions following a switch to oral therapy represents another potential
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20 benefit from the patient perspective.
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25 A number of assumptions employed in the model have the potential to alter the results in either
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27 direction. It was assumed that oral tablets were dispensed in 3-month supplies by the pharmacy
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29 rather than monthly refills, which would be expected to underestimate the cost-saving potential
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31 of oral therapy if not all patients opt for quarterly refills. Underestimation of savings may have
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33 also occurred as a result of calculating tablet cost based on non-generic products at higher
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35 costs per tablet. Home care costs for the administration of B₁₂ injections in home-bound patients
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37 was not included since the proportion of patients receiving in-home injections was unknown,
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39 and it was assumed that these injections would be administered in conjunction with a regular
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41 visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits
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43 are indeed being performed for B₁₂ injections, then the savings of switching to oral B₁₂ would
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45 obviously be greater. Importantly, the model also assumed that all patients making the switch to
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47 oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore
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49 representing maximum saving potential. This assumption is consistent with previously published
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51 randomized controlled trials and case series reporting treatment success across all patients
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53 studied [32-98]. Additionally, we assumed in the base scenario that additional laboratory
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55 monitoring is only required for the first year following the switch to oral therapy, with monitoring
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3 as usual for the remaining years. Considering that adherence to self-administered oral therapy
4 may be lower than a healthcare professional-administered injection, even if an additional set of
5 laboratory tests were performed each year for the 5-year term of the model, estimated cost
6 savings would still amount to \$12 million.
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14 Direct comparison between our model and the results of the 2001 cost-saving paper cannot be
15 performed due to differing model assumptions and available data. Overall, both models report
16 significant cost-saving potential of the switch from the perspective of a government payer over
17 five years. However, due to higher current professional fees for injection administration, our
18 model found overall cost-savings even if no additional physician visits occurred for patients
19 receiving B₁₂ injections, whereas the previous study found a break-even point when 16.3% of
20 additional physician visits were avoided.
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31 The use of cost-minimization analysis is controversial as it assumes equal efficacy and
32 tolerability between the two options being compared; however, we feel this assumption is
33 justifiable based on published data comparing the oral and intramuscular routes [32-98].
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38 However, the total number of patients studied in the randomized trials (total n=141 across 3
39 studies) and case series (n=151) remains relatively small and doses employed across each
40 study differed. Further research on a larger population, comparing standard-dose IM therapy to
41 standard-dose oral therapy is therefore recommended and is currently being planned.
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46 Additionally, payers considering adding oral B₁₂ tablets to their formularies should consider
47 allowing for the coverage of intramuscular therapy in the event of documented treatment failure
48 on oral supplementation, until larger-scale studies confirming equivalence are conducted, or
49 allowing for short-term IM therapy for patients with neurologic symptoms followed by oral
50 maintenance therapy. Indeed, a planned randomized controlled trial of 320 patients age ≥65 in
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Spain will be directly comparing oral to IM B₁₂ and is expected to examine non-inferiority of oral therapy over one year (clinicaltrials.gov NCT01476007).

Overall, our model estimates that \$8-24 million in cost-savings can be realized over five years if all Alberta seniors currently receiving IM vitamin B₁₂ are switched to oral therapy. Within closed systems like universal healthcare, this is unlikely to represent true cost savings, but rather room for re-allocation of resources to other health system needs. With an aging population and increasing rates of chronic disease, switching of patients from IM to oral vitamin B₁₂ replacement appears to be not only clinically efficacious, but also an effective use of limited healthcare resources.

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REFERENCES

1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. J Am Med Assoc 1991;**265**:94-5.
2. Bethell FH, Castle WB, Conley CL. Present status of treatment of pernicious anemia: Ninth announcement of the U.S.P. Anti-Anemia Preparations Advisory Board. J Am Med Assoc 1959;171(15):2092-4.
3. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. Blood 1998;**92**(4):1191-1198.

- 1
2
3 | ~~3.4.~~ Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. Oral versus
4 | intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective,
5 | randomized, open-label study. *Clin Ther* 2003;**25**(12):3124-3134.
6
7
8
9
10 | ~~4.5.~~ Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, et al. Comparing
11 | the Efficacy and Tolerability of a New Daily Oral Vitamin B12 Formulation and Intermittent
12 | Intramuscular Vitamin B12 in Normalizing Low Cobalamin Levels: A Randomized, Open-
13 | Label, Parallel-Group Study. *Clin Ther* 2011;**33**(3):358-71.
14
15
16
17
18 | ~~5.6.~~ Nyholm E, Turpin P, Swain D, Cunningham B, Daly S, Nightingale P, et al. Oral vitamin
19 | B12 can change our practice. *Postgrad Med J* 2003;**79**:218-220.
20
21
22
23 | ~~6.7.~~ Vidal-Alaball J, Butler C, Cannings-John R, Goringe A, Hood K, McCaddon A, et al. Oral
24 | vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane*
25 | *Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD004655.
26 | DOI:10.1002/14651858.CD004655.pub2.
27
28
29
30
31 | ~~7.8.~~ Kwong JC, Carr D, Dhalla IA, Tom-Kun D, Upshur REG. Oral vitamin B12 therapy in the
32 | primary care setting: a qualitative and quantitative study of patient perspectives. *BMC Fam*
33 | *Pract* 2005;**6**:8.
34
35
36
37
38 | ~~8.9.~~ Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of
39 | vitamin B12 without intrinsic factor. *Acta Med Scand* 1968;**184**:247-58.
40
41
42
43 | ~~9.10.~~ Graham ID, Jette N, Tetroe J, Robinson N, Milne S, Mitchell SL. Oral cobalamin remains
44 | medicine's best kept secret. *Archives of Gerontology and Geriatrics* 2007;**44**(1):49-59.
45
46
47 | ~~10.11.~~ MacFarlane AJ, Greene-Finestone LS, Shi Y. Vitamin B-12 and homocysteine status in
48 | a folate-replete population: results from the Canadian Health Measures Survey. *Am J Clin*
49 | *Nutr* 2011;**94**:1079-87.
50
51
52
53 | ~~11.12.~~ Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of
54 | cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;**60**:2-11.
55
56
57
58
59
60

- 1
2
3 | ~~12-13.~~ de Jager J, Kooy A, Lehert P, Wulffele MG, van der Kolk J, Bets D, et al. Long term
4 | treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency:
5 | randomized placebo controlled trial. Br Med J 2010;**340**:c2181.
6
7
8
9
10 | ~~13-14.~~ Andrès E, Vidal-Alaball J, Federici L, Henoun Loukili N, Zimmer J, Kaltenbach G. Clinical
11 | aspects of cobalamin deficiency in elderly patients. Epidemiology, causes, clinical
12 | manifestations, and treatment with special focus on oral cobalamin therapy. Eur J Int Med
13 | 2007;**18**:456-62.
14
15
16
17
18 | ~~14-15.~~ Andrès E, Federici L, Affenberger S, Vidal-Alaball J, Henoun Loukili N, et al. B12
19 | deficiency: A look beyond pernicious anemia. J Fam Pract 2007;**56**(7):537-42.
20
21
22
23 | ~~15-16.~~ Health Canada. Dietary Reference Intakes: Reference Values for Vitamins. Accessed 17
24 | May 2012 at <http://www.hc-sc.gc.ca/fnan/nutrition/reference/table/ref_vitam_tbl-eng.php>.
25
26
27
28 | ~~16-17.~~ van Walraven CG, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements:
29 | How much money could be saved by switching from injections to pills? Can Med Assoc J
30 | 2001;**47**:79-86.
31
32
33
34 | ~~17-18.~~ Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district
35 | nurse. BMJ 1985;**270**:1254-1255.
36
37
38 | ~~18-19.~~ Drummond MF, Sculpher MJ, Torrance G, O'Brien B, Stoddart G. Methods for the
39 | Economic Evaluation of Health Care Programmes. 3rd ed. New York: Oxford University
40 | Press; 2005.
41
42
43
44 | ~~19-20.~~ IMS Brogan LRx database, January 2013 and Compuscript audit, January 2013.
45
46
47 | ~~20-21.~~ Alberta Health. Pharmacy fee reimbursement. Retrieved from:
48 | <http://www.health.alberta.ca/services/pharmacy-fee-reimbursement.html>
49
50
51 | ~~21-22.~~ Alberta Health. Coverage for Seniors. Retrieved from:
52 | <http://www.health.alberta.ca/services/drugs-seniors.html>
53
54
55 | ~~22-23.~~ Alberta Health. Interactive Drug Benefit List. Retrieved from:
56 | <https://idbl.ab.bluecross.ca/idbl/load.do>
57
58
59
60

- 1
2
3 | 23-24. Government of Alberta. 2011 Alberta Wage and Salary Data – Medical Laboratory
4 |
5 | Technologist. Retrieved from:
6 |
7 | [http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=ht](http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140)
8 |
9 | [ml&occpro_id=71003140](http://alis.alberta.ca/occinfo/content/requestaction.asp?aspaction=gethtmlprofile&format=html&occpro_id=71003140)
10 |
11 |
12 | | 24-25. *Guidelines for the economic evaluation of health technologies: Canada* [3rd Edition].
13 |
14 | Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
15 |
16 | | 25-26. Alberta Health Care Insurance Plan. Medical Price List as of 01 April 2012. Retrieved
17 |
18 | from: <http://www.health.alberta.ca/documents/SOMB-Medical-Prices-2012-04.pdf>
19 |
20 |
21 | | 26-27. Alberta Health. Compensation for Pharmacy Services, July 2012. Retrieved from:
22 |
23 | <http://www.health.alberta.ca/documents/Pharmacy-Services-Compensation-2012.pdf>
24 |
25 | | 27-28. Hauber AB, Johnson FR, Sauriol L, Lescrauwaet B. Risking health to avoid injections:
26 |
27 | Preferences of Canadians with type 2 diabetes. *Diabetes Care* 2005;28(9):2243-5.
28 |
29 |
30 |
31 |
32 |
33 |
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EVEREST Statement

	Study section	Additional remarks
Study design		
(1) The research question is stated	Background	
(2) The economic importance of the research question is stated	Background	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods (Study Type); Discussion	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Background; Methods	
(5) The alternatives being compared are clearly described	Methods (Cost Determination)	
(6) The form of economic evaluation used is stated	Methods (Study Type)	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Methods; Discussion	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods (Study Type)	
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A (based on multiple studies)	3 randomized controlled trials and 2 prospective case series
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods (Primary Outcome)	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	Methods (Setting/Patients)	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods (Cost Determination)	
(17) Methods for the estimation of quantities and unit costs are described	Methods (Cost Determination)	
(18) Currency and price data are recorded	Methods (Primary Outcome)	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	

(20) Details of any model used are given	Methods (Model Assumptions, Discounting, Sensitivity Analyses)	
(21) The choice of model used and the key parameters on which it is based are justified	Methods (Study Type); Discussion	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods (Study Type)	
(23) The discount rate(s) is stated	Methods (Discounting)	
(24) The choice of rate(s) is justified	Methods (Discounting)	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods (Sensitivity Analyses)	
(28) The choice of variables for sensitivity analysis is justified	Methods (Sensitivity Analyses)	
(29) The ranges over which the variables are varied are stated	Table 1	
(30) Relevant alternatives are compared	Introduction	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	N/A	
(33) The answer to the study question is given	Results; Discussion	
(34) Conclusions follow from the data reported	Discussion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	