Testosterone Replacement Therapies: A Drug Class Review

Final report and reimbursement option recommendations

December 2014
Ontario Drug Policy Research Network
The Ontario Drug Policy Research Network (ODPRN) is funded to conduct drug class reviews as part of an initiative to modernize the public drug formulary in Ontario. As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP), Ministry of Health and Long-Term Care to select key priority areas and topics for formulary modernization, then conducts independent drug class reviews and disseminates the results of each of these reviews directly to the OPDP to facilitate informed decision making on public drug funding policies.

Conflict of Interest Statement
Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada.
Paul Oh was a member of an advisory board for Amgen, Astra Zeneca, Janssen, Novartis, Pfizer, Roche and Sanofi.
Tara Gomes received grant funding from the Ministry of Health and Long-term Care.

No other study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the Testosterone Replacement Therapy Drug Class Review.

Acknowledgments
This review was funded by grants from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund and Drug Innovation Fund. The work was also supported by The Keenan Research Centre of St. Michael’s Hospital (SMH), the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute sponsored by the Ontario MOHLTC, and by the Canadian Institute for Health Information (CIHI). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources and supporting organizations. No endorsement by SMH, ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred.

Study Team
- Formulary Modernization Team: Paul Oh, Sandra Knowles
- Qualitative Team: Alekhya Mascarenhas, Radha Sayal, Sobia Khan, Julia E. Moore from the Knowledge Translation Program at the Li Ka Shing Knowledge Institute
- Systematic Review Team: George Wells, Jesse Elliott, Shannon Kelly, Joan Peterson, Amy Johnston, Ahmed Kotb, Li Chen, Becky Skidmore
- Pharmacoeconomics Team: Diana Martins, Kimberly Fernandes, Zhan Yao, Samantha Singh, Baiju Shah, Sandra Knowles, David Juurlink, Muhammad Mamdani, Mina Tadrous, Tara Gomes
- Pharmacoepidemiology Team: Doug Coyle, Karen Lee, Kelley-Anne Sabarre, Kylie Tingle
- Research Team, Clinical Experts: Adam Millar, Kirk Lo, Robert Lam
- Research Team, Patient Representative: Gus De Bruyne
- Research Team, Representative from Committee to Evaluate Drugs: Baiju Shah

Note
Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AB</td>
<td>Alberta</td>
</tr>
<tr>
<td>BC</td>
<td>British Columbia</td>
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<tr>
<td>CAN</td>
<td>Canadian/Canada</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CIHI</td>
<td>Canadian Institute for Health Information</td>
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<td>CP</td>
<td>Citizens’ Panel</td>
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<tr>
<td>EAP</td>
<td>Exceptional Access Program</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<td>FDA</td>
<td>Food Drug Administration</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>ICES</td>
<td>Institute for Clinical Evaluative Sciences</td>
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<tr>
<td>IM</td>
<td>Intramuscular</td>
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<tr>
<td>LU</td>
<td>Limited Use</td>
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<tr>
<td>MB</td>
<td>Manitoba</td>
</tr>
<tr>
<td>MOHLTC</td>
<td>Ministry of Health Long-Term Care</td>
</tr>
<tr>
<td>NB</td>
<td>New Brunswick</td>
</tr>
<tr>
<td>NIHB</td>
<td>Non-Insured Health Benefits</td>
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<tr>
<td>NL</td>
<td>Newfoundland</td>
</tr>
<tr>
<td>NMA</td>
<td>Network meta-analysis</td>
</tr>
<tr>
<td>NS</td>
<td>Nova Scotia</td>
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<td>NU</td>
<td>Nunavut</td>
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<tr>
<td>NW</td>
<td>Northwest Territories</td>
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<tr>
<td>ODB</td>
<td>Ontario Drug Benefit</td>
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<td>ON</td>
<td>Ontario</td>
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<tr>
<td>OPDP</td>
<td>Ontario Public Drug Programs</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PEI</td>
<td>Prince Edward Island</td>
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<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
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<tr>
<td>Q1</td>
<td>First quarter</td>
</tr>
<tr>
<td>QC</td>
<td>Quebec</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SK</td>
<td>Saskatchewan</td>
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<tr>
<td>SMH</td>
<td>St. Michael’s Hospital</td>
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<tr>
<td>TRT</td>
<td>Testosterone replacement therapy</td>
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<td>YK</td>
<td>Yukon Territories</td>
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Executive Summary
Testosterone replacement therapy (TRT) is indicated for the treatment of hypogonadism. There are several formulations of TRT products available in Canada: oral, long-acting injectables, and various topical products (i.e., gel, patch, solution). In Ontario, all commercially available products (with the exception of Axiron and Androgel pump) are available as Limited Use on the Ontario Drug Benefit (ODB) formulary.

As part of the formulary modernization review, an evaluation of testosterone replacement products for the management of patients with hypogonadism was undertaken to provide funding and policy recommendations of these products in Ontario.

Key Considerations for Reimbursement Options

Efficacy and Safety
A total of 39 randomized controlled trials were identified in our systematic review, of which almost half were conducted in older men. TRT products as a class were shown to increase serum testosterone. However, for the efficacy outcomes related to quality of life, erectile dysfunction, libido or depression, no statistically significant effect of TRT was identified.

Meta-analyses were conducted for safety outcomes of cardiovascular death, myocardial infarction, stroke, prostate cancer, and serious adverse events associated with TRT. No statistically significant findings were observed in these safety outcomes, with the exception of cardiovascular death, although the number of events was extremely small and these findings should be interpreted with caution.

Accessibility
No current accessibility issues were identified in this review. However, concern has been raised regarding the rise in utilization of TRT products, in particular the use of topical products in men 65 years and older, despite no apparent increase in the prevalence of classic hypogonadal conditions (e.g., androgen deficiency due to disorders of the hypothalamic-pituitary-testicular axis). In Ontario, there may be approximately 40-80% of men currently using TRT who may not meet the Limited Use (LU) Criteria; approximately one-third of new testosterone users had no lab test for testosterone levels in the year prior to their first prescription for therapy despite the LU criteria requiring that serum testosterone levels are required prior to initiation of TRT. Note that patients tested in hospital laboratories were not captured in the analysis, and therefore the number of laboratory tests may be underestimated.

In 2012, there were 14,701 TRT users covered under Ontario Public Drug Programs (OPDP). Proposed Exceptional Access Program (EAP) strategies for TRT products suggest a possible decrease in number of users ranging from 7-46% based on experience from other provinces with similar access policies and depending on the reimbursement strategy adopted.

Pharmacoconomics
Projected cost analyses based on various hypothetical reimbursement models were performed to
determine the economic impact. Proposed EAP strategies for TRT products suggest a reduction in total TRT costs ranging from 20-43% ($2.4-5.2 million).

**Reimbursement Options**

Given the lack of clear clinical benefit, possible safety signal, increasing and potentially inappropriate utilization and costs associated with testosterone therapies, four main reimbursement options for TRTs are proposed.

**Option A: Limited Use Listing for all TRT Products (i.e., no change from current listing)**
- TRT products (all formulations) listed as Limited Use on the ODB formulary.

**Option B: Exceptional Access Program (EAP) for all TRT Products**
- **Rationale:** An increase in utilization for TRT was observed, driven in large part by topical formulations. No significant difference noted between products in terms of efficacy or safety. Projected impact of this option is a 46% decrease in number of users with a decrease in expenditures of approximately 43%.
- TRT products (all formulations as currently listed on the ODB formulary) covered under ODB’s EAP program.
- Restriction criteria for EAP include:
  - Male patients with confirmed low morning serum testosterone levels
  - Patients with documented, symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients.

**Option C: Exceptional Access Program (EAP) for Topical and Oral TRT Products, LU listing for Injectable TRT Products**
- **Rationale:** A large increase in utilization with topical TRT was observed as compared to oral and injectable products. As well, the cost of topical and oral TRT products is greater than injectable TRT. Option C represents a balance between accessibility of testosterone (via injectable) and potential misutilization of the newer formulations. Projected impact of this option is a 15% decrease in number of users with a decrease in expenditures of approximately 30%.
- Oral and topical TRT products (currently listed on the ODB formulary) covered under the ODB’s EAP program.
- Injectable TRT products listed as Limited Use on the ODB formulary.
- Restriction criteria for EAP and LU include:
  - Male patients with confirmed low morning serum testosterone levels
  - Patients with documented, symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients.

**Option D: Exceptional Access Program (EAP) for Topical TRT Products, LU listing for Oral and Injectable TRT Products**
- **Rationale:** A large increase in utilization with topical TRT was observed as compared to oral and
injectable products. The cost of injectable and oral products is less than topical TRT. Option D represents a balance between accessibility of testosterone (via injectable and oral) and potential misuse utilization of the newer formulations. Projected impact of this option is a 7% decrease in number of users with a decrease in expenditures of approximately 20%.

- Topical TRT products (currently listed on the ODB formulary) covered under the ODB’s EAP program.
- Oral and injectable TRT products listed as Limited Use on the ODB formulary.
- Restriction criteria for EAP and LU include:
  - Male patients with confirmed low morning serum testosterone levels
  - Patients with documented, symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients.

Findings from the ODPRN Citizens’ Panel

Citizens’ Panel members rated each of the policy options on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint. The final rankings were as follows:

1. Option C: EAP for oral and topical, LU for injectable
2. Option B: EAP for all products
3. Option D: EAP for topical, LU for injectable and oral
4. Option A: LU for all products

Recommendation

Testosterone replacement products, currently listed as Limited Use in Ontario, are indicated for the treatment of hypogonadism. Although all public plans in Canada provide coverage for at least one TRT product for eligible patients, most plans have restricted the use of the topical products or do not fund these formulations; the injectable is available as a general benefit in most jurisdictions. Results from our systematic review indicate that TRT products have limited clinical efficacy and data on safety, including cardiovascular safety, are often conflicting. Concern has been raised regarding the rise in utilization of TRT products, in particular the use of topical products in men 65 years and older. As well, there may be as many as 80% of men currently using TRT who do not meet the Limited Use criteria. Based on the results of the review, input from stakeholders and feedback from the ODPRN Citizens’ Panel, three primary reimbursement options for testosterone replacement therapies are recommended as funding alternatives for the Ontario Public Drug Program:

- EAP for all TRT products
  OR
- EAP for Topical and Oral TRT products, LU listing for Injectable TRT products
  OR
- EAP for Topical TRT products, LU listing for injectable and oral TRT products
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Concern has been raised regarding the rise in the utilization of TRT products despite no apparent increase in the prevalence of classic hypogonadal conditions (i.e., androgen deficiency due to disorders of the hypothalamic-pituitary-testicular axis). A recent study highlighted the increased use of TRTs in Ontario, in particular the increased utilization of topical products in men 65 years and older. The potential benefits of testosterone have not been confirmed in any large-scale, long-term clinical trial. In addition, safety concerns have been identified including potential association with cardiovascular adverse events (e.g., myocardial infarction and stroke) and prostate cancer.

As part of the formulary modernization review, an evaluation of TRT products for the management of patients with hypogonadism was undertaken to provide funding and policy recommendations in Ontario.

This report outlines the key findings for each of the components of the review. More detailed information for each of the reviews can be found on the ODPRN website: www.odprn.ca

Background Information
Testosterone replacement therapy (TRT) has been available in Canada since the 1950s for the treatment of men with conditions associated with a deficiency or absence of endogenous testosterone (i.e., hypogonadism). Hypogonadism results from testicular failure (e.g., Klinefelter syndrome, testicular tumors-referred to as primary hypogonadism), or is due to hypothalamic-pituitary dysfunction (e.g., hyperprolactinemia, Kallmann syndrome-referred to as secondary hypogonadism), or both (e.g., late-onset hypogonadism). Although the use of TRT for the treatment of primary and secondary hypogonadism (“classic hypogonadism”) is considered standard of care, controversy still exists regarding treatment of aging men who have low serum testosterone due to the process of aging, and have nonspecific symptoms (e.g., fatigue, decreased in sexual function, decrease in bone mineral density, muscle mass and strength). This is referred to as “andropause” or “age-related hypogonadism”. Nonspecific age-related symptoms and low testosterone levels may be present in older men without a clear causal link to any pathology.

Primary hypogonadism is uncommon. Klinefelter syndrome, the most frequent form of primary hypogonadism, affects approximately 0.2% (about 1 in 600 live births) of the male population. Testicular tumors occur in about 12 per 100,000 males; approximately 25% of these patients have testosterone deficiency after treatment. Forms of secondary hypogonadism include Kallmann syndrome (prevalence 1 in 10,000), Prader-Willi syndrome (prevalence 1 in 10,000), congenital adrenal hypoplasia with hypogonadotropic hypogonadism (prevalence 1 in 12,500 individuals),
hyperprolactinemia (caused by prolactin-secreting pituitary adenomas or drug-induced), non-functioning pituitary adenomas and post-pituitary surgery.\textsuperscript{6} The prevalence of unequivocal hypogonadism (testosterone less than 6 nmol/L) is reported as 6.3\% in a survey conducted in the UK.\textsuperscript{9} The prevalence of late-onset hypogonadism is not well defined, and has varied from 2 to 40\%\textsuperscript{10-12} depending on various factors including the population studied and the definition of hypogonadism. It should be noted that testosterone levels decline approximately 1-2\% per year after age 40 and may fall below the lower limit of the normal range for younger, healthy men. The age-related decline is affected by comorbidities, including chronic disease (e.g., HIV disease, diabetes mellitus), adiposity and medications.\textsuperscript{13}

**Treatment strategies**

TRT is used in men with a confirmed diagnosis of hypogonadism. TRT is used to establish and maintain secondary sexual characteristics, sexual function, body composition and quality of life.\textsuperscript{7} The target testosterone concentration is individualized, but the goal is to achieve levels in the mid-normal range. Controversy still exists regarding reference ranges for normal levels of testosterone. As well, interlaboratory variability and use of different assays may lead to diverse reference ranges across laboratories. Most guidelines suggest that total testosterone level above 12 nmol/L does not require replacement; patients with serum levels below 8 nmol/L have been found to benefit from treatment.\textsuperscript{13,14} The lower limit of the normal range for young men is considered to be approximately 10.4 nmol/L, with men having a greater likelihood of having symptoms below this threshold than above it.\textsuperscript{13} It is recommended that testosterone levels (at least two morning levels obtained between 0700-1100hr) be measured prior to commencement of TRT.\textsuperscript{13}

Several products are available in Canada, and differ in their route of administration, pharmacokinetics and formulation. Selection of a product is often influenced by factors such as patient preference, pharmacokinetics of the testosterone formulation, treatment burden, cost and adverse effects. All TRT products, regardless of formulation, are federally designated controlled substances. Under Ontario’s Narcotics Safety and Awareness Act 2010, the Ministry of Health Long-Term Care requires the collection and disclosure of personal health information to monitor prescribing, dispensing and to ensure the appropriate use of testosterone and other controlled substances.\textsuperscript{15} Intramuscular testosterone esters (testosterone enanthate and cypionate) are long-acting preparations that are administered every 2-3 weeks, with peak concentrations occurring shortly after injection and gradual decline after 7-15 days.\textsuperscript{5} Oral testosterone (testosterone undecanoate) requires multiple, daily doses with intake of fatty food due to low bioavailability.\textsuperscript{5} There are four topical TRT products available in Canada that are applied once daily: testosterone transdermal patch (Androderm), testosterone 1\% topical gel (Testim), testosterone 1\% gel (via foil packet or metered-dose pump) (Androgel) and testosterone 2\% topical solution (Axiron).
Public plan reimbursement of TRT products in Canada

TRT products (namely: Androgel [gel packet only], Testim, Androderm, testosterone cypionate [Depo-Testosterone], testosterone enanthate [Delatestryl] and testosterone undecanoate capsules [Andriol and generics]) are available as Limited Use products in Ontario since 2005. Prior to that date, they were all available as general benefit on the ODB formulary. Axiron (testosterone topical solution) and Androgel pump are currently not listed on the ODB formulary. The Limited Use criteria for TRT products states that: For male patients with confirmed low morning serum testosterone levels associated with documented, symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients. Note: Older males with nonspecific symptoms of fatigue, malaise, depression who have a low normal random testosterone level do not satisfy these criteria.

Although all public plans in Canada provide coverage for at least one TRT product for eligible patients, most plans have restricted the use of the topical products. Five of the 12 (42%) public drug programs in Canada do not list topical TRT products on their formulary. Five provinces list the topical products on a restricted basis (i.e., requiring prior authorization). Quebec lists the topical TRT products as a general benefit. Although restriction criteria vary among the public drug plans, most state that the TRT products are indicated for treatment of congenital and acquired primary or secondary hypogonadism in males. Five jurisdictions, including Ontario, specifically state that these products are not considered for use in the treatment of androgen decline in the aging male.

### Exhibit 1: Public plan listings in Canada for TRT products

<table>
<thead>
<tr>
<th>Drug</th>
<th>BC</th>
<th>AB</th>
<th>SK</th>
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<th>ON</th>
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<td></td>
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<tr>
<td>testosterone undecanoate</td>
<td>No</td>
<td>Res</td>
<td>Ben</td>
<td>Ben</td>
<td>Pas</td>
<td>Ben</td>
<td>Res</td>
<td>Ben</td>
<td>Res</td>
<td>Ben</td>
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<td>Long-acting injectable</td>
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<td>testosterone cypionate</td>
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<td>Ben</td>
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<td>Pas</td>
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<td>No</td>
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</tr>
</tbody>
</table>

No=not listed; Res=restricted listing – enforced; Pas= restricting listing – passive; Ben=unrestricted listing

### Objective

The objective of testosterone replacement therapy drug class review is to provide evidence-informed recommendations for the funding of these products through the publicly funded drug program in Ontario.
Components of the Drug Class Review
The comprehensive approach to TRT drug class review is comprised of:

- qualitative analyses of perspectives of patients and prescribers
  - one-on-one semi-structured telephone interviews regarding specific experiences and perceptions relevant to funding policies for TRTs
- environmental scans of:
  - national and international drug policies
  - considerations relating to health equity,
- analysis of real-world drug utilization using:
  - administrative claims data from Ontario and across Canada
  - summaries of relevant observational literature,
- systematic review of the literature,
- reimbursement-based economic analyses and cost-effectiveness literature review.

Results from all of the above components were reviewed and consolidated into a set of options for potential drug reimbursement models.

Overview of Findings

Qualitative Research Team: Perspectives of Patients and Healthcare Providers

Diagnosis of hypogonadism can be complex
Although participants perceived that TRT is an accepted treatment for individuals with exceptionally low testosterone levels, there was no consensus on the appropriateness of TRT for men who do not present with this condition. Clinicians stated that the condition of hypogonadism is not well understood and can be a consequence of a variety of health conditions. As well, the administration and interpretation of testosterone tests varied between physicians. There was a range of perceptions of the purpose of TRT, how it should be used and the balance of risks versus benefits of treatment.

“While we are potentially trying to increase access for patients who truly need it, we gotta think, if we flood the market with this product, what are the long term consequences? We really have no idea, there is no study that is over 3 years of testosterone supplement.” - Urologist

Multiple factors that influence formulation choices
Decision making about formulation selection revolve around the affordability of products based on the level of coverage available for TRT; some patients with partial or no coverage prefer the injectable products over others because they are the most affordable. As well, other factors that were considered in formulation selection included the patient and physician preferences regarding the various TRT formulations, mostly relating to ease of use, perception of efficacy, consistency of testosterone levels, and market availability of TRT.

“One of the important issues is cost. Some of them are very expensive [especially if the patient] requires large amounts of testosterone, others are less expensive. Most of them are covered by plans but sometimes you have patients who are not covered by any plan” - Urologist
Access to TRT products
Our qualitative analysis found that access to TRT is impacted by a number of important factors at the patient and provider levels. For example, patient access to information regarding the risks and side effects is less available than information about benefits. As well, patients may access TRT by being persistent in obtaining these medications. Finally, physicians’ prescribing habits can facilitate or hinder access to TRT, depending on the physician's philosophy toward the drugs. With regard to accessing publicly funded TRT for patients, physicians in our sample had little knowledge of the LU code criteria for obtaining TRT through the OPDP, and also felt that the criteria needed to be clarified to be applied correctly.

“I know when I was talking to another friend of mine, when he wanted it I think he got it without the test, but that’s because he put up a big stink about it.” - Patient

Pharmacoepidemiology Team

Current Utilization in Canada and Ontario
Prescriptions for TRT products in Canada have increased by almost 40% over the last 4 years, from 99,854 prescriptions in the last quarter of 2009 to 137,318 prescriptions by the first quarter (Q1) of 2014, the majority of which were for topical formulations (46%). During this time there has been no change in the approved indications for TRT nor has there been an increase in the prevalence of classic hypogonadal conditions for which TRT is approved.4

There was wide variation in the utilization of provincially-funded TRT prescriptions dispensed across provinces (from 76 [PEI] to 702 [Alberta] prescriptions per 100,000 eligible population, in Q1 2014). The low rate of TRT prescriptions in PEI may reflect the restrictive access of these medications (only the injectable testosterone is available as a general benefit) through the public drug program (see Exhibit 2). By the first quarter of 2014, Ontario had the fourth highest rate of provincially-funded TRT use (508 prescriptions per 100,000 eligible population compared to the national average of 489 prescriptions per 100,000 eligible population) and highest costs of provincially-funded TRT products ($57,519 per 100,000 eligible population compared to the national average of $44,192 per 100,000 eligible population (data not shown)). This may be due to the high use of topical TRT in Ontario (see Exhibit 3), which is the most costly TRT formulation. The overall monthly average cost per user for topical TRT (excluding the patch and Axiron) ($115.80) was substantially higher than injectable TRT ($24.80).
Exhibit 2: Population-adjusted utilization of provincially-funded TRT in Canada by province

Exhibit 3: Provincial rate of topical TRT use among public drug plan beneficiaries 65+ years
Over half of TRT prescriptions in Ontario are paid for through non-public drug coverage (52%). Non-provincially-funded TRT use in Ontario was on par with the national average (226 prescriptions per 100,000 eligible population compared to the national average of 252 prescriptions per 100,000 eligible population in Q1 2014) (see Exhibit 4).

Exhibit 4: Population-adjusted utilization of non-provincially-funded TRT in Canada by province

TRT Patterns of Use in Ontario
Between April 2008 and March 2013, almost half of all male beneficiaries aged 66 and older, who were new users of provincially-funded TRT products in Ontario, were treated with topical gel testosterone (see Exhibit 5). This was followed by oral testosterone, injectable testosterone and transdermal testosterone patch. Transdermal patches were minimally used in Ontario as well as other provinces in Canada.

Among new users, the majority had more than one prescription; however almost half of users initiating injectable testosterone had only one prescription. Among the patients who had more than one prescription for TRT, adherence to therapy was highest among those prescribed oral testosterone, followed by topical gel testosterone, injectable testosterone and transdermal patch testosterone (p<0.001). Studies that have evaluated adherence and/or persistence with TRT (both topical and injectable formulations) have shown inconsistent results, with some indicating poor adherence (i.e., 15% by 12 months) and other showing high adherence patterns (e.g., 91% after 12 months).16-19
A documented diagnosis of hypogonadism through claims data was low among new testosterone users; between 9.5% and 14.5% of testosterone users had a documented diagnosis of hypogonadism. Note that the diagnosis codes have not been validated for hypogonadism. Approximately one-third of new testosterone users had no lab test for testosterone levels in the year prior to their first prescription for therapy. However, this ranged (between 25-40%) depending on TRT formulation initiated, with topical TRT users more likely to have had past testosterone level lab tests compared to oral and injectable users. Note that patients tested in hospital laboratories were not captured in our analysis, and therefore the number of laboratory tests may be underestimated. Our results are similar in other jurisdictions. For example, in the United Kingdom, 54% of patients initiated on TRT did not have a testosterone measurement in the 180 days before initiation. Results from a population-based cohort study from Manitoba showed that 83% of their study population did not have a testosterone measurement prior to initiation of therapy.

Testosterone users had similar comorbidities across formulation groups, although the incidence is higher than reported in the general population. In testosterone users 65 years and older, 74% had a history of hypertension and almost 40% had a past diagnosis of diabetes. In comparison, only 33% of men under the age of 65 years had a history of hypertension and almost 25% had a past history of diabetes.
Rapid Review Team

Efficacy
A total of 39 unique randomized controlled trials (RCTs) were identified in the systematic review in 55 publications. The total number of participants in studies ranged from 10 to 406, with an overall number of included participants of 3243. Participants ranged in age from 20 to 95 years.

There was substantial heterogeneity in the populations of the RCTs. For example, of the RCTs that were included in the review, a total of 30 trials were focused in older men (with or without co-morbidities), 5 studies involved HIV-infected patients, 4 in men with erectile dysfunction, 1 in patients with classic hypogonadism as well as late-onset hypogonadism, and 11 included men with other conditions (e.g., depression, Alzheimer’s). Network meta-analyses (NMA) and pair-wise meta-analysis were conducted for five efficacy outcomes: serum testosterone level, quality of life, erectile dysfunction, libido and depression. The choice of these outcomes was based on input from stakeholder groups (e.g., researchers, healthcare providers) and the sufficiency of the data available to derive robust and consistent network models.

The results of the analysis were as follows (see Exhibit 6 and 7):

- **Serum testosterone**
  - Several of the TRT products were associated with a substantive increase in serum testosterone levels at 3 months, in particular: Androderm patch, Androgel 1% gel, Testim 1% gel plus sildenafil, Delatestryl and testosterone enanthate IM.
  - Within class comparisons, the largest increase in serum testosterone was for Androgel 1% gel and Delatestryl (IM, 200 mg/2wk). Andriol (oral, 120 mg/d) was associated with less favourable serum testosterone levels at 3 months than the other TRTs.
  - Note that there were no studies involving Axiron were eligible for inclusion.

- **Quality of life:**
  - Overall, no significant improvements in quality of life were identified.

- **Erectile dysfunction:**
  - No significant improvements in erectile dysfunction were identified.

- **Libido:**
  - Overall no significant improvements in libido were identified.

- **Depression:**
  - No significant effects on depression were identified.
### Exhibit 6: Serum testosterone level, quality of life, erectile dysfunction, libido, and depression: mean differences from placebo based on network meta-analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean difference (SD)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum testosterone</td>
<td>Quality of life</td>
<td>Erectile dysfunction</td>
<td>Libido</td>
</tr>
<tr>
<td>level, 3 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androderm, patch, 5 mg/d</td>
<td>5.38 *</td>
<td>---</td>
<td>---</td>
<td>-0.94</td>
</tr>
<tr>
<td>Androgel 1%, gel, 50 mg/d</td>
<td>10.38 *</td>
<td>1.53</td>
<td>3.29</td>
<td>-1.65</td>
</tr>
<tr>
<td>Androgel 1%, gel, 100 mg/d</td>
<td>18.49 *</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Testim 1%, gel, 50–150 mg/d + sildenafil</td>
<td>10.24 *</td>
<td>1.05</td>
<td>1.40</td>
<td>0.28</td>
</tr>
<tr>
<td>Testim 1%, gel, 50 mg/d</td>
<td>2.28</td>
<td>---</td>
<td>---</td>
<td>-0.14</td>
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<tr>
<td>Androgel 1%, gel, 75 mg/d</td>
<td>7.53 *</td>
<td>2.49</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Andriol, oral, 120 mg/d</td>
<td>-4.34</td>
<td>---</td>
<td>---</td>
<td>0.97</td>
</tr>
<tr>
<td>Delatestryl, IM, 200 mg/2wk</td>
<td>15.67</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Testosterone enanthate, IM, 100 mg/wk</td>
<td>6.30</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Testosterone enanthate, IM, 200 mg/2wk</td>
<td>8.65</td>
<td>---</td>
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</tr>
<tr>
<td>Testosterone cypionate, IM, 200 mg/2wk</td>
<td>-0.18</td>
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</tr>
<tr>
<td>Andriol, oral, 160 mg/d</td>
<td>---</td>
<td>-0.77</td>
<td>-0.13</td>
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<td>Testim 1%, gel, 100 mg/d</td>
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<td>---</td>
<td>0.51</td>
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<td>Andriol, oral, 120–160 mg/d</td>
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<td>-18.78</td>
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<tr>
<td>Testosterone undecanoate, oral, 160 mg/d</td>
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<td>-0.29</td>
<td>3.62</td>
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</tr>
<tr>
<td>Andriol, oral, 40 mg/d</td>
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<tr>
<td>Testosterone enanthate, IM, 300 mg/3wk</td>
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<td>---</td>
</tr>
<tr>
<td>Androgel 1%, gel, 5 mg/d</td>
<td>---</td>
<td>-3.16</td>
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</tr>
</tbody>
</table>

Note: IIEF = International Index of Erectile Function, IM = intramuscular injection, SD = standard deviation, SMD = standardized mean difference.

1. SMD translated to Aging Male Symptoms (AMS) Rating Scale.
2. SMD translated to IIEF erectile dysfunction domain.
3. SMD translated to IIEF sexual desire domain.
4. SMD translated to Beck Depression Inventory.

*Statistically significant (p < 0.05).

Despite the lack of significant findings for the outcomes of quality of life, erectile dysfunction, libido and depression, some individual RCTs reported significant results. For example, no significant improvements in quality of life were identified in our analysis pooling trial data; only one study out of 10 RCTs found a significant improvement in quality of life. As well, for the outcome of libido, no significant improvements were identified when we pooled data from trials; three of 9 studies found a significant difference in libido, two found a deterioration in libido for TRT and one study involving men with type II diabetes found an improvement compared to placebo. In general, systematic reviews and meta-analysis, are considered more robust in their findings than individual randomized controlled trials.
**Exhibit 7: Head-to-head comparisons of TRTs on serum testosterone level at 3 months**

<table>
<thead>
<tr>
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<th>3</th>
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</table>

* For serum testosterone level at 3 months:
  - The green block indicates that the ‘row’ treatment is significantly better than the ‘column’ treatment.
  - The red block indicates that the ‘row’ treatment is significantly worse than the ‘column’ treatment.
  - The grey block indicates that there is no significant difference between the ‘row’ and ‘column’ treatment.

**Treatments:**

1. Androderm, patch, 5 mg/d
2. Androgel 1%, gel, 50 mg/d
3. Androgel 1%, gel, 100 mg/d
4. Testim 1%, gel, 50–150 mg/d + sildenafil
5. Testim 1%, gel, 50 mg
6. Androgel 1%, gel, 75 mg/d
7. Andriol, oral, 120 mg/d
8. Delatestryl, IM, 200 mg/2wk
9. Testosterone enanthate, IM, 100 mg/wk
10. Testosterone enanthate, IM, 200 mg/2wk
11. Testosterone cypionate, IM, 200 mg/2wk

**Safety and tolerability**

A number of safety outcomes were studied: cardiovascular death, myocardial infarction, stroke, erythrocytosis, serious adverse events, newly diagnosed disease (diabetes, heart disease, prostate cancer), and skin or site reactions. No NMA was completed for any of the safety outcomes either due to the rarity of the events and/or the study treatments were too variable.

Meta-analyses (treatment vs. placebo) were conducted for cardiovascular death, myocardial infarction, stroke, prostate cancer, and serious adverse events. No statistically significant findings were observed in the safety outcomes, with the exception of cardiovascular death, where there was an indication of a possible relationship with TRT. In two studies there were 4 events in the testosterone gel group and zero in the placebo group, resulting in an overall odds ratio (OR) of 8.62 (95% confidence interval [CI] 1.17-63.77). Due to the limited amount of information contributing to this outcome, results from the meta-analysis of cardiovascular death should be interpreted with caution.

**Skin reactions**

Skin-related adverse events reported in RCTs ranged from mild skin irritation to rashes. These reactions were found to present as from allergic contact dermatitis and moderate skin erythema to intense edema and blistering. In non-randomized studies, skin reactions were found to be similar (e.g., application site reaction, urticarial, acne, erythema).
Other safety studies

Non-randomized and observational studies: Data from eight non-randomized studies were reviewed. Prostate cancer was reported in six studies, erythrocytosis in two studies, and cardiovascular events in two studies. Skin reactions were assessed in three studies.

Safety data from non-randomized trials were limited and poorly reported:

- Cardiovascular death: not reported
- Myocardial infarction: reported in 1 study (1 event in treatment group, 0 in control)
- Stroke: 1 study (1 event in treatment group, 1 in control)
- Diabetes: 1 study (1 event in treatment group, 0 in control)
- Erythrocytosis: 2 studies (11 events in treatment group, 0 in control)
- Prostate cancer: 5 studies (unable to tabulate due to poor reporting)

Systematic reviews and meta-analyses: There have been several meta-analyses published that have investigated the risk of a cardiovascular-related event in association with TRT. These meta-analyses included men who were either eugonadal or hypogonadal, in contrast to our review which only included men with total testosterone levels ≤12 nmol/L. In one systematic review and meta-analysis comprising 27 published RCTs representing 2,994 men, TRT increased the risk of a cardiovascular-related events (OR 1.54, 95% CI 1.09 to 2.18). However, other meta-analyses did not find any increase in cardiovascular risk associated with TRT. For example, a meta-analysis showed that TRT was not associated with any significant difference in the incidence of major adverse cardiovascular event with respect to placebo (OR 1.01, 95% CI 0.57-1.77). Therefore, the review of the literature as well as our own meta-analysis has shown conflicting results regarding a potential association between TRT and cardiovascular adverse events.

A systematic review of RCTs and observational studies in eugonadal or hypogonadal men was conducted to determine possible adverse effects of TRT. In this study, TRT was associated with a significant increase in hemoglobin and hematocrit, and a decrease in high-density lipoprotein cholesterol. However, no significant effect was noted on mortality, prostate or cardiovascular outcomes.

Hepatotoxicity: Hepatotoxicity has been described with methyltestosterone and fluoxymesterone, two oral agents that are no longer available in Canada. Testosterone derivatives that have been associated with liver toxicity contain an alkyl group in the C17 position. In contrast to these older agents, testosterone undecanoate lacks the alkyl group at the C17 position. There are no studies that suggest an increased risk of hepatotoxicity with this agent, compared to other testosterone products. Intramuscular injections and topical preparations do not appear to be associated with hepatic dysfunction.

Health Canada warning

Health Canada issued an information update on July 15, 2014 advising the community of new safety information regarding testosterone hormone replacement products and risk of serious and possible life-
threatening cardiovascular problems. Health Canada completed a safety review and found evidence for serious and possible life-threatening cardiovascular problems. They noted that testosterone products:

- Should not be used in men for non-specific symptoms if laboratory tests have not been done to confirm a low testosterone level and other possible causes for the symptoms have not been excluded
- Should not be used in children under the age of 18 as safety and effectiveness has not been established in these patients
- Should not be used by women

The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee completed a review and concluded that there was not consistent evidence to show that testosterone increases the risk of cardiovascular problems. The United States Food and Drug Administration (FDA) is investigating the risk of stroke, heart attack and death in men taking testosterone products.

**Pharmacoeconomics Team**

**Cost-effectiveness Literature Review**

A total of 57 published economic analyses of testosterone use were identified for potential inclusion in the report; of these, only one study met the criteria for inclusion in this review. This economic evaluation was a cost-utility analysis comparing testosterone undecanoate depot injection (not commercially available in Canada) to no treatment in patients with Klinefelter syndrome and in patients with late-onset hypogonadism, aged 20-88 years.

For the treatment of Klinefelter syndrome, the incremental cost utility ratio of testosterone undecanoate versus no treatment was $24,617 per quality adjusted life year (QALY) in $CAN 2014 [1€=1.4709 $CAN] from a health care payer perspective and $31,333 per QALY in $CAN 2014 from a societal perspective. For the treatment of late onset hypogonadism, the incremental cost utility ratio of testosterone undecanoate versus no treatment was $18,346 per QALY in $CAN 2014 from a health care payer perspective and $36,596 per QALY in $CAN 2014 from a societal perspective.

Major limitations with this study with respect to the assumptions relating to treatment effectiveness and the applicability of the analysis to the Canadian context were noted. As such, no inferences regarding the cost-effectiveness of TRT can be made to the Canadian context.

**Reimbursement-Based Economic Assessment**

In 2013, Ontario Public Drug Plan (OPDP) expenditure on TRT was $8.3 million ($3.4 million for patients < 65 years and $4.9 million for patients ≥ 65 years). Overall, expenditure on TRT expenditure was the greatest at $5.3 million. Without any changes to current TRT reimbursement, TRT expenditure is expected to surpass $9.5 million by 2014 and $12.2 million by 2016. Although the analysis did not include the costs associated with any increase in the volume of testosterone tests, the low costs of tests (ranging from approximately $14-$40) compared with the ongoing costs of drug treatment would suggest that this would have little impact on forecasted expenditures.
Reimbursement strategies (See Exhibit 8 and 9) considered in the analysis included:
- No change in listing (i.e., all products remain Limited Use listing)
- All products to EAP
- Oral and topical products to EAP, injectables remain LU
- Topical products to EAP, oral and injectables remain LU

Under EAP, criteria for reimbursement of TRT considered patients who are HIV positive or patients with a positive laboratory test result for hypogonadism. In general, the overall rate of use of TRT products under EAP was estimated by assuming that the rate of use per beneficiary will be the lesser of the current rate in Ontario or the combined rate in Manitoba and Nova Scotia where there is restricted access to topical products.

Option A: No change in listing of TRT products
- Without any changes to current TRT reimbursement, TRT expenditure is expected to surpass $12.2 million by 2016 ($5.2 million for patients <65 years and $7.0 million for patients ≥ 65 years).
- The number of forecasted users per quarter (2016) is 16,069 (<65: 7,208; 65+: 8,861).
  - The number of new users in 2016 is forecasted at 2700.

Option B: All TRT products under proposed EAP
- Moving all TRT formulations under EAP would lead to an overall reduction of 42.9% or savings of $5.2 million by 2016.
- It is estimated that this would lead to a 45.6% reduction in number of users compared to no change in listing (i.e., all products remain LU).

Option C: Oral and topical TRT products under proposed EAP
- Injectable TRT products remain under LU listing.
- Moving oral and topical TRT products under EAP would lead to an overall reduction of 31.8% or savings of $3.9 million, respectively, by 2016.
- It is estimated that this would lead to a 14.7% reduction in number of users compared to no change in listing.

Option D: Topical TRT products under proposed EAP
- Injectable and oral products would remain under LU listing.
- Moving only topical forms of TRT under EAP would result in an overall reduction of 20.0% or savings of $2.4 million respectively by 2016.
- It is estimated that this would lead to a 6.6% reduction in number of users compared to no change in listing.
### Exhibit 8: Budget Impact Analysis

<table>
<thead>
<tr>
<th>Options for Reimbursement</th>
<th>Total Costs and Impact on TRT budget (2016)</th>
<th>% Budget Impact</th>
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<tbody>
<tr>
<td>Current Reimbursement of all TRT therapy (2013)</td>
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<tr>
<td><strong>Option A: All testosterone replacement therapy products listed as Limited Use (LU)</strong></td>
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<tr>
<td>65+ years</td>
<td>Expected total $</td>
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<tr>
<td>&lt;65 years</td>
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<tr>
<td>Total: all patients</td>
<td>Expected total $</td>
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</tr>
<tr>
<td>Budget impact</td>
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<tr>
<td><strong>Option B: All TRT products under EAP</strong></td>
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<tr>
<td>65+ years</td>
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<td>&lt;65 years</td>
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<td>Budget impact</td>
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<td><strong>Option C: Topical and oral products under EAP, injectable LU listing</strong></td>
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<td>-$1,464,641</td>
<td></td>
</tr>
<tr>
<td>TOTAL: all patients</td>
<td>Expected total $</td>
<td>$8,322,567</td>
</tr>
<tr>
<td>Budget impact</td>
<td>-$3,887,457</td>
<td></td>
</tr>
<tr>
<td><strong>Option D: Topical TRT products under EAP, oral and injectable LU listing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65+ years</td>
<td>Expected total $</td>
<td>$5,407,006</td>
</tr>
<tr>
<td>Budget impact</td>
<td>-$1,572,464</td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>Expected total $</td>
<td>$4,365,919</td>
</tr>
<tr>
<td>Budget impact</td>
<td>-$864,635</td>
<td></td>
</tr>
<tr>
<td>Total: all patients</td>
<td>Expected total $</td>
<td>$9,772,925</td>
</tr>
<tr>
<td>Budget impact</td>
<td>-$2,437,099</td>
<td></td>
</tr>
</tbody>
</table>
## Exhibit 9: Summary of Budget Impact Analysis (for 2016)

<table>
<thead>
<tr>
<th></th>
<th>Option A All TRT products listed as Limited Use (LU)</th>
<th>Option B All TRT products under EAP</th>
<th>Option C Topical and oral TRT products under EAP, injectable LU listing</th>
<th>Option D Topical TRT products under EAP, oral and injectable LU listing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forecasted # users per quarter</td>
<td>16,069</td>
<td>8,749</td>
<td>13,711</td>
<td>15,016</td>
</tr>
<tr>
<td>Change in # of users per quarter</td>
<td>NA</td>
<td>-7,320</td>
<td>-2,358</td>
<td>-1,053</td>
</tr>
<tr>
<td>% change in # users</td>
<td>NA</td>
<td>↓45.6%</td>
<td>↓14.7%</td>
<td>↓6.6%</td>
</tr>
<tr>
<td>Total costs</td>
<td>$12,210,024</td>
<td>$6,968,801</td>
<td>$8,322,567</td>
<td>$9,772,925</td>
</tr>
<tr>
<td>Impact on TRT budget</td>
<td>NA</td>
<td>-$5,241,223</td>
<td>-$3,887,457</td>
<td>-$2,437,099</td>
</tr>
<tr>
<td>% budget impact</td>
<td>NA</td>
<td>↓42.9%</td>
<td>↓31.8%</td>
<td>↓20.0%</td>
</tr>
</tbody>
</table>

### Health Equity Issues

No major health equity issues were identified in this review. See
Appendix A for Health Equity Considerations.

**Accessibility of Testosterone Replacement Therapies**
Currently, all TRT products (with the exception of Axiron and Androgel pump) are listed as Limited Use products in Ontario. No accessibility issues were identified in our review for men who meet the LU criteria. Factors that were considered in formulation selection included the patient and physician preferences regarding the various TRT formulations, mostly relating to ease of use, cost, perception of efficacy, consistency of testosterone levels, and market availability of TRT.

There was data to indicate that there may be inappropriate use of TRT products in some patients. Our analysis showed that less than 15% of testosterone users had a documented diagnosis of hypogonadism, despite this being the main criterion for TRT reimbursement. In addition, only two-thirds of new testosterone users had a lab test for testosterone levels in the year prior to their first prescription for therapy; however, the LU criteria specifically state that serum testosterone levels are required prior to initiation of TRT. Anecdotal evidence obtained through the qualitative analysis suggests that some patients may facilitate access to TRT by being persistent in obtaining these medications.

**Use in elderly**
Overall, just over half of males treated with provincially-funded TRT products were aged 65 years and older. The majority of older testosterone users were using topical testosterone (43%).

**Reimbursement Options for Consideration**

**Key Considerations**

**Efficacy**
- Overall, a statistically significant increase in serum testosterone was noted at 3 months of treatment with TRT, in particular Androgel 1% and Delatestryl (200mg every 2 weeks).
- However, no significant improvements in quality of life, erectile dysfunction, libido or depression were identified in the analyses for TRT products.

**Safety and Tolerability**
- Meta-analyses were conducted for cardiovascular death, myocardial infarction, stroke, prostate cancer, and serious adverse events. No statistically significant findings were observed in the safety outcomes, with the exception of cardiovascular death, where there was an indication of a possible relationship with TRT.
- Our systematic review of RCTs and non-randomized trials has shown conflicting results regarding a potential association between TRT and cardiovascular adverse events.
- Health Canada reviewed TRT products for cardiovascular risk and concluded that there is the possibility that cardiovascular risk may increase with TRTs.
Accessibility and Utilization

- No current accessibility issues were identified in this review. Proposed EAP strategies for TRT products would limit use of TRT only for patients who meet the criteria (see Appendices B and C).
- Selection of a product is influenced by factors such as patient preference, treatment burden, cost and adverse effects.
- Testosterone utilization in Canada has increased 37.5% over a five-year period, from 2009 to 2014. In particular, substantial increases (approximately 60%) were seen for injectable and topical products.
  - Ontario's public drug program has seen topical testosterone utilization rates increase 29-fold over a 7-year period (from 2005 to 2012).
- In Ontario, some data suggest that there may be inappropriate use of TRT products in some patients who do not meet the current Limited Use criteria.
  - Less than 20% of testosterone users had a documented diagnosis of hypogonadism, using claims data; note that diagnosis codes have not been validated for hypogonadism.
  - Approximately one-third of new testosterone users had no lab test for testosterone levels in the year prior to their first prescription for therapy. Note that patients tested in hospital laboratories were not captured in our analysis, and therefore the number of laboratory tests may be underestimated.
- In 2012, there were 14,701 users of TRT under OPDP. Proposed EAP strategies for TRT products suggest a decrease in number of users ranging from 7-46%, depending on the inclusion of oral or injectable products under the EAP program.

Pharmacoeconomics

- Proposed EAP strategies for TRT products suggest a reduction in total TRT costs ranging from 20-43% ($2.4-$5.2 million), depending on the inclusion of oral and/or injectable products (in addition to topical products) under the EAP program.
- The monthly average cost per user for the topical products (excluding the patch and Axiron) is greater than either the injectable or oral products ($115.80 vs. $24.77 and $65.16, respectively). Note that this represents drug costs only and excludes other healthcare-related costs (e.g., physician visit for administration of injectable TRT).

Reimbursement Options

Given the lack of clear clinical benefit, possible safety signal, increasing and potentially inappropriate utilization and costs associated with TRT, four main reimbursement options for TRT are proposed.

Option A: Limited Use Listing for all TRT Products (i.e., no change from current listing)

- TRT products listed as Limited Use on the ODB formulary.
- Includes all formulations as currently listed on ODB formulary: oral testosterone, topical testosterone (Androgel foil packets, Testim, Androderm), injectable testosterone

Option B: Exceptional Access Program (EAP) for all TRT Products
• Rationale: An increase in utilization for TRT was observed, driven in large part by the topical products. No significant difference noted between products in terms of efficacy or safety. Projected impact of this option is a 46% decrease in number of users with a decrease in expenditures of approximately 43%.
• TRT products covered under the ODB’s EAP program.
• Includes all formulations as currently listed on ODB formulary: oral testosterone, topical testosterone (Androgel foil packets, Testim, Androderm), injectable testosterone
• Restriction criteria for EAP include:
  o Male patients with confirmed low morning serum testosterone levels
  o Patients with documented, symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients.

Option C: Exceptional Access Program (EAP) for Topical and Oral TRT Products, LU listing for Injectable Testosterone Products
• Rationale: A large increase in utilization with topical TRT was observed as compared to oral and injectable products. As well, the cost of topical and oral TRT products is greater than injectable TRT. Option C represents a balance between accessibility of testosterone (via injectable) and potential misutilization of the newer formulations. Projected impact of this option is a 15% decrease in number of users with a decrease in expenditures of approximately 30%.
• Oral and topical testosterone products (as currently listed on ODB formulary) covered under the ODB’s EAP program.
• Injectable testosterone products listed as Limited Use on the ODB formulary.
• Restriction criteria for EAP and LU include:
  o Male patients with confirmed low morning serum testosterone levels
  o Patients with documented, symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients.

Option D: Exceptional Access Program (EAP) for Topical TRT Products, LU listing for Oral and Injectable TRT Products
• Rationale: A large increase in utilization with topical TRT was observed as compared to oral and injectable products. The cost of injectable and oral products is less than topical TRT. Option D represents a balance between accessibility of testosterone (via injectable and oral) and potential misutilization of the newer formulations. Projected impact of this option is a 7% decrease in number of users with a decrease in expenditures of approximately 20%.
• Topical TRT products (as currently listed on ODB formulary) covered under the ODB’s EAP program.
• Oral and injectable TRT products listed as Limited Use on the ODB formulary.
• Restriction criteria for EAP and LU include:
  o Male patients with confirmed low morning serum testosterone levels
  o Patients with documented, symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients.
Stakeholder Review
Findings from the stakeholder review contributed to selection of final policy recommendations, and include feedback solicited from an open call for review, comments received during a workshop for stakeholders, as well as results from the ODPRN Citizen’s Panel.

Findings from the ODPRN Citizens’ Panel
Citizens’ Panel (CP) members rated each of the policy options on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint. Through one teleconference meeting and two rounds of an online survey, CP members voiced the following perceptions:

- Option A (LU option): was considered too liberal, especially in light of potential safety risks, lack of evidence for efficacy and burden to the health care system
- Option B (EAP for all products): considered a good option, although increased restrictiveness may deter some physicians from prescribing TRT to those with valid indications
- Option C (EAP for topical and oral and LU for injectable TRT): was the most acceptable option
- Option D (EAP for topical, LU for injectable and oral products): was considered too accessible given the concerns regarding safety, efficacy and cost
Exhibit 1: Final Ranking of Policy Options

<table>
<thead>
<tr>
<th>Option</th>
<th>Final Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Option C: EAP for oral and topical, LU for injectable</td>
<td>1</td>
</tr>
<tr>
<td>Option B: EAP for all TRT products</td>
<td>2</td>
</tr>
<tr>
<td>Option D: EAP for topical, LU for injectable and oral</td>
<td>3</td>
</tr>
<tr>
<td>Option A: Limited Use for all TRT products</td>
<td>4*</td>
</tr>
</tbody>
</table>

Note that the most consensus was reached with regard to Option A (LU for all products), where all Citizens’ Panel member respondents (n=8, 100%) ranked this option as the least acceptable option.

**Final Policy Recommendations and Conclusion**

Testosterone replacement products, currently listed as Limited Use in Ontario, are indicated for the treatment of hypogonadism. Although all public plans in Canada provide coverage for at least one TRT product for eligible patients, most plans have restricted the use of the topical products or do not fund these formulations; the injectable is available as a general benefit in most jurisdictions. Results from our systematic review indicate that TRT products have limited clinical efficacy and data on safety are often conflicting. Concern has been raised regarding the rise in utilization of TRT products, in particular the use of topical products in men 65 years and older. As well, there may be as many as 80% of men currently using TRT who do not meet the Limited Use criteria. Based on the results of the review, input from stakeholders and feedback from the ODPRN Citizens’ Panel, three primary reimbursement options for testosterone replacement therapies are recommended as funding alternatives for the Ontario Public Drug Program:

- EAP for all TRT products
  - OR
- EAP for Topical and Oral TRT products, LU listing for Injectable TRT products
  - OR
- EAP for Topical TRT products, LU listing for injectable and oral TRT products
## Exhibit 10: Assessment of Reimbursement Options

<table>
<thead>
<tr>
<th></th>
<th>Option A: Limited Use (no change in listing)</th>
<th>Option B: EAP for all products</th>
<th>Option C: EAP for topical and oral, LU for injectable</th>
<th>Option D: EAP for topical, LU for oral and injectable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Data is limited to indicate that TRT products are efficacious for outcomes of quality of life, libido, erectile dysfunction, and depression</td>
<td>Possible increase in cardiovascular events with TRT; with EAP listings, a small number of patients exposed to TRT products</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety concerns</strong></td>
<td>Possible increase in cardiovascular events with TRT; however, LU listing exposes the greatest number of patients to TRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Accessibility</strong></td>
<td>No change in number of patients currently receiving TRT</td>
<td>↓45.6% in number of users**</td>
<td>14.7% decrease in number of users**</td>
<td>6.6% decrease in number of users**</td>
</tr>
<tr>
<td><strong># of users potentially eligible for EAP</strong></td>
<td>Not applicable</td>
<td>Based on 2016 projections, approximately 1600 new patients may apply to the EAP program.</td>
<td>Based on 2016 projections, approximately 1250 new patients may apply to the EAP program.</td>
<td>Based on 2016 projections, approximately 800 new patients may apply to the EAP program.</td>
</tr>
<tr>
<td><strong>Budget Impact (2016 annual expenditures estimated $12.2 million)</strong></td>
<td>No change</td>
<td>Cost savings of 43% (savings of $5.2 million)</td>
<td>Cost savings of 32% (savings of $3.9 million)</td>
<td>Cost savings of 20% (savings of $2.4 million)</td>
</tr>
<tr>
<td><strong>Alignment with other jurisdictions</strong></td>
<td>Quebec (general listing)</td>
<td>BC†</td>
<td>PEI, NL, NB</td>
<td>NIHB††, YK††, MB††, SK††</td>
</tr>
<tr>
<td><strong>Prescribing Criteria</strong></td>
<td>Unenforced prescribing criteria</td>
<td>Enforced prescribing criteria used</td>
<td>Enforced criteria used for topical and oral, unenforced prescribing criteria for injectables</td>
<td>Enforced criteria used for topical, unenforced prescribing criteria for injectables and oral</td>
</tr>
<tr>
<td><strong>Indication creep</strong></td>
<td>Unenforced restriction criteria via LU listing may result in continued or even increased use of TRT for patients who do</td>
<td>Indication creep unlikely due to individual clinical review</td>
<td>Indication creep unlikely for topical and oral products due to individual clinical review</td>
<td>Indication creep unlikely for topical products due to individual clinical review</td>
</tr>
</tbody>
</table>
not meet LU criteria.

* current annual expenditures approximately $8.3 million

**In 2012 there were 14,701 users of testosterone under the OPDP program.
†BC does not provide coverage for oral or topical products; injectable products are available under Special Authorization.
††These jurisdictions do NOT provide coverage for topical products; oral and injectable are listed as general benefits
Reference List


(3) Nigro N, Christ-Crain M. Testosterone treatment in the aging male: myth or reality? *Swiss medical weekly* 2012; 142.


endocrinology and metabolism 2010; 95:2536-2359.


## Appendix A: Health Equity Considerations for Testosterone Replacement Therapy Drug Class Review

<table>
<thead>
<tr>
<th>Populations</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboriginal peoples (e.g., First Nations, Inuit, Métis, etc.)</td>
<td>No accessibility issues identified. Coverage of medications, including TRT, for aboriginal peoples is available through Ontario Ministry of Health and Long-term Care.</td>
</tr>
<tr>
<td>Age-related groups (e.g., children, youth, seniors, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>Disability (e.g., physical, D/deaf, deafened or hard of hearing, visual, intellectual/developmental, learning, mental illness, addictions/substance use, etc.)</td>
<td>No accessibility issues identified. Patients with disability and receiving Ontario Disability Support Program Income Support, receive prescription drug coverage (including TRT) through ODB.</td>
</tr>
<tr>
<td>Ethno-racial communities (e.g., racial/racialized or cultural minorities, immigrants and refugees, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>Francophone (including new immigrant francophones, deaf communities using LSQ/LSF, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>Homeless (including marginally or under-housed, etc.)</td>
<td>Not eligible for ODB coverage.</td>
</tr>
<tr>
<td>Linguistic communities (e.g., uncomfortable using English or French, literacy affects communication, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>Low income (e.g., unemployed, underemployed, etc.)</td>
<td>No accessibility issues identified; low income individuals who receive public drug coverage will have access to TRT through ODB.</td>
</tr>
<tr>
<td>Religious/faith communities</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>Rural/remote or inner-urban populations (e.g., geographic or social isolation, under-serviced areas, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>Sex/gender (e.g., male, female, women, men, trans, transsexual, transgendered, two-spirited, etc.)</td>
<td>This drug class review only considered the use of testosterone in males. No accessibility issues identified in the review.</td>
</tr>
<tr>
<td>Sexual orientation, (e.g., lesbian, gay, bisexual, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>Other: please describe the population here.</td>
<td>None identified.</td>
</tr>
</tbody>
</table>

## Appendix B: Assessment of Criteria for Coverage (for both LU and EAP Listing)

<table>
<thead>
<tr>
<th>Criteria (for testosterone use)</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use in male patients</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|                                 | This review did not evaluate the efficacy or safety of TRT in women.  
|                                 | All TRT products are only indicated for males in the product monographs.  
|                                 | Use in males encompasses the large majority of use of TRT products.  
|                                 | Health Canada’s warning stated that testosterone products should not be used in women.² | The use of TRT in women is limited to very specific indications (e.g., inoperable metastatic breast cancer). |
| **Confirmed low morning serum testosterone levels** | All guidelines recommend that a diagnosis of hypogonadism is made based on signs and symptoms and low morning serum testosterone levels. ⁶,¹³,¹⁴  
|                                 | At least two testosterone measurements are needed to diagnose androgen deficiency.⁷ | Definition of "low" serum testosterone level (<8 nmol/L OR <6.9 nmol/L) and the type of testosterone test recommended (total testosterone) are not standardized in guidelines. However, there is some suggestion that a level of 10.4 nmol/L may correspond to the lower limit of normal range for young men.¹³  
|                                 | Interlaboratory variability observed with testosterone levels.⁴⁰  
|                                 | The use of free testosterone measurements by analog methods (used in most laboratories in Ontario) is not recommended as measurements are affected by alterations in sex hormone binding globulin (SHBG).¹³ |
| **Patients with**               | In non placebo-controlled studies, testosterone | There may be other groups of patients for whom |

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² Health Canada. (2008). Health Canada's warning stated that testosterone products should not be used in women.  
⁴⁰ Interlaboratory variability observed with testosterone levels.
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| hypothalamic, pituitary or testicular disease OR HIV-infected patients (with weight loss) | therapy in classic hypogonadal patients results in improvements in some symptoms.  
In a systematic review of RCTs of TRT in HIV-infected men with weight loss, greater gains in body weight were seen with TRT than placebo.  
TRT may be indicated (e.g., drug-induced hypogonadism related to opioid use). | |
| Symptomatic patients                         | All guidelines recommend that a diagnosis of hypogonadism is made based on signs and symptoms and low serum testosterone levels.  
The number of signs/symptoms required for a diagnosis is not well-defined, although 3 signs/symptoms have been suggested. | |
| NOT TO BE USED: older male patients with nonspecific symptoms of fatigue, malaise, depression | Endocrine society guidelines do not recommend testosterone therapy to all older men with low testosterone levels.  
Results from our NMA do not indicate that quality of life (e.g., fatigue, malaise) nor depression are improved with TRT. | |
Appendix C: Proposed Limited Use/Exceptional Access Program Criteria

Criteria for Coverage

1. Male patient with confirmed low morning serum testosterone levels on at least 2 different dates in the previous 12 months (levels required)
   a. total serum testosterone level less than 10.4 nmol/L OR
   b. bioavailable testosterone level below the normal range for the laboratory

AND

2. a. Patient with congenital or acquired primary or secondary hypogonadism with a specific diagnosis of:
   i. Primary: cryptorchidism, Klinefelter’s, orchiectomy or other established causes
   ii. Secondary: pituitary-hypothalamic injury due to tumors, trauma, radiation or other established causes

OR

b. HIV-infected patients with AIDS-wasting syndrome

AND

3. Documented clinical signs and symptoms consistent with androgen deficiency

Exclusion

1. Older male patients with nonspecific symptoms such as fatigue, malaise, depression who have a normal testosterone level

Duration of Approval

Unlimited

Notes

1. Testing of serum total testosterone should be done when patients are clinically stable; avoid testing during acute illness.

2. Free testosterone measurements by analog methods (used in most laboratories in Ontario) may be inaccurate and their use is not recommended. Similarly, the free androgen index (simple ratio of testosterone and SHBG concentrations) is considered an unreliable index of bioavailable testosterone.

3. Monitoring of treatment:
   a. The monitoring of testosterone therapy is primarily clinical (i.e., patient has improvement in symptoms), and should be done at 3-6 months after start of treatment and annually thereafter.
   b. Testosterone levels should be repeated 3-6 months after initiation of therapy. It is recommended that serum testosterone levels during treatment be in the mid-normal range.
   c. Other monitoring parameters can include: assessment of hematocrit, bone mineral density in hypogonadal men with osteoporosis or low trauma fracture, and prostate safety (e.g., digital rectal examination of prostate and prostate specific antigen (PSA)).