ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Treatment for Overactive Bladder

Stakeholder Review #1: Information Session

July 2015

GENERAL

Comment: Stakeholder feedback is limited to 5 pages. Does this limit apply to the evidence submission package?

Response: *Comments will need to be limited to 5 pages, however this limit does not include evidence submission packages. Evidence submission packages (included published/unpublished work) can be longer.*

Comment: Has the Information Session for review of the draft reports and recommendations been scheduled as yet?

Response*: No, the second Information Session has not been scheduled as yet. This is partially due to the fact that the timelines may change as the review progresses. Notifications will be communicated to stakeholder groups once the second Information Session has been scheduled.*

Comment: Will concomitant therapies be considered in any of the analyses?

Response: *The Pharmacoepidemiology Unit will be examining some concomitant therapy use among current OAB users. External stakeholders are encouraged to submit drug classes that they would like the ODPRN to consider when examining concomitant therapy.*

Comment: There are some inconsistencies across research plans regarding the drugs included in the analysis.

- **It is not clear that Botox is included in all of the research or only in portions of the research.**
- **The full list of dosage forms are listed for some products but not for others (e.g., tolterodine vs. fesoteridine).**
- **Transdermal OAB products do not seem to be captured in the analysis plans (i.e., Gelnique).**
- **If combination treatment is going to be evaluated, then all potential combinations should be included to ensure consistency (this needs to be more clearly/consistently defined in all protocols).**

Response:

a. Botulinum toxin is included in the various research teams' proposals. For the pharmacoepidemiology team, Botox use will only be included among individuals using OAB agents. For the systematic review team, Botox is considered a comparator as part of the PICO statement.

b. All dosage forms (long-acting, transdermal) will be included in the analyses for the teams, whenever possible.

c. The primary goal of this review is to examine efficacy and safety of pharmacologic treatments for OAB with the goal of informing reimbursement decisions. As such, the

treatments considered for reimbursement are monotherapy. We are aware that the combination of mirabegron and solifenacin specifically may be considered for patients with tolerability limitations to higher dose antimuscarinics and that there are Phase II to IV studies of mirabegron as an add-on therapy to antimuscarinic agents. We will consider combinations only if a de novo systematic review is conducted and the comprehensive research plan has been amended to reflect this change.

Comment: **Suggest that the "other" category be separated into beta-3 adrenergic agonists (mirabegron) and neuromuscular blockers (onabotulinumtoxinA). The current approach incorrectly implies that these products are in the same category. It would be helpful to readers to more specifically and clearly define the different mechanisms of action for all of the classes of medication used in the treatment of OAB.**

Response: *The "other" category has been subdivided into beta-3 adrenergic agonists and neuromuscular blockers.*

Comment: **Recommend that the final reports generated by ODPRN clearly articulate any limitations related to the methodologies used, to help decision makers determine how the results may inform their decision processes.**

Response: *At the end of the review period, each team will produce a report that will include a section on "limitations", specifically highlighting limitations related to methodologies used.*

Qualitative Research Team

Comment: **How do you obtain information related to newly listed products from patient/prescriber interviews?**

Response: *Our interview guide includes questions on the use of specific medications, including newly listed OAB products. We will use various recruitment strategies to try and attract a diverse group of participants including patients who have used newer products.*

Comment: **We are pleased to see that patient groups will be included in both the policy feasibility assessment portion as well as the front-end qualitative data collection process, given that they are directly impacted by any proposed policies that may be developed.**

Response: *Thank you. We are committed to engaging in an integrated approach to knowledge translation where we involve all relevant stakeholders (e.g. patients, clinicians) throughout the research process.*

Comment: **The sample size seems small for health care professionals; and, the selection criteria should be clarified to include physicians who are regularly engaged in the treatment of OAB.**

Response: *Qualitative research studies tend to comprise smaller samples than quantitative studies. Currently, there are no strict guidelines that outline exactly how many participants are sufficient to ensure a robust qualitative analysis[1]; this assessment is often made by the researchers throughout the research process using the following decision criteria:*

- *Feasibility – what is the time frame available for participant recruitment?*
- *Heterogeneity – how diverse is the group we are recruiting?*
- *Saturation of data – have we captured as many unique themes as possible about the phenomenon being studied?*

The National Centre for Research Methods in the United Kingdom has recommended that qualitative researchers who have 8-16 weeks for recruitment should aim for a sample of approximately 12[2]. An American study on qualitative methods also concluded that saturation of themes can occur after 12 interviews and as early as 6 interviews[1]. Also, keeping in mind that the goal of qualitative studies is not to generalize, but rather to reach saturation of themes; therefore when working with a relatively homogenous group of participants 6-8 participants may be sufficient to reach saturation of themes[3].

References

1. Guest, Greg, Bunce, Arwen, and Johnson, Laura. How many interviews are enough? *An experiment with data saturation and variability*. Field Methods, Vol. 18, No. 1, (2006) 59–82
2. Baker, Sarah Elsie and Edwards, Rosalind (2012) *How many qualitative interviews is enough.*
3. *Kuzel AJ. Sampling in qualitative inquiry. In: Crabtree BF, Miller WL, eds. Doing qualitative research (second edition). Thousand Oaks, Calif: Sage Publications; 1999:33-45.*

Systematic Review Unit

Comment: **There are several products that have been on the market for a long period of time. Since the systematic reviews will only include literature from 2000 onwards, how will the older data be considered?**

Response: *Thank you for your question. We have reconsidered the date limitation we proposed in our draft comprehensive research plan and following consultation with clinical experts, have moved the date back to January 1, 1990. We are hoping that we are able to find a high-quality systematic review that will capture all primary studies back to this date. In the event that we are unable to find such a review, we will perform a de*

novo review of studies back to this date (to ensure the capture of all relevant oxybutynin studies with treatment regimens clinically relevant to current practice.)

Comment: Urgency is also an important outcome measure in OAB for treatment efficacy assessment, as emphasized in clinical practice guidelines in this therapeutic area. In fact, urgency may be as/more important than incontinence from a patient perspective. It should be included as one of the key outcome measures evaluated.

Response: *Thank you for your input. We are limited in the number of outcomes we are able to analyze and collect as part of this rapid review of evidence. As the current list of outcomes has been discussed with the research team and clinical experts, we would need to consider the opportunity cost of including this outcome at the expense of another. We agree that this is an important outcome and will consult with clinical experts to determine if the outcomes for the project should be changed.*

Comment: Mean volume voided is an important endpoint in this therapeutic area, as it provides a reliable measure of bladder capacity and bladder function. It should be more clearly spelled out as one of the urodynamic measures included in the evaluation.

Response: *Thank you for your input. We limited in the number of outcomes we are able to analyze and collect as part of this rapid project and have tried to prioritize outcomes that will inform the reimbursement decisions, the pharmacoeconomics model and which are important to patients. Following consultation with clinical experts, we have removed urodynamic measures from the PICO in order to prioritize some of the key outcomes needed for the project.*

Comment: Cognitive decline/effects are an important safety outcome measure to assess in this therapeutic areas, as is the risk of falls (i.e., two separate outcomes, although in some cases they can be related).

- **Both are implied outcomes, as reflected in ODPRN's intention of looking at subpopulations in long-term care (e.g., looking at risk of falls in elderly).**
- **Some studies show that OAB is an independent risk factors for falls in the elderly, and effective treatment of OAB can actually decrease the risk of falls.**
- **In addition, the medications used to treat OAB in the past have been identified as creating risks for older patients (see Beer's list, etc. in reference list submitted).**
- **Useful to more clearly articulate cognitive effects as a key outcome measure, considering the related comments that have been flagged by CDEC in previous OAB reviews.**

Response: *Thank you for your comments. We are limited in the number of outcomes we are able to analyze and collect as part of this rapid review of evidence. We have amended our*

subgroups to include two age categories above age 65 and 75 to capture important differences in efficacy and harms following a consultation with clinical experts. As the current list of outcomes has been discussed with the research team and clinical experts, we would need to consider the opportunity cost of including cognition and fall outcomes at the expense of other outcomes. We will consult with clinical experts to determine if the outcomes for the project should be changed.

Comment: Quality of life is an important consideration for patients with overactive bladder and should be included as an outcome measure.

Response: *Thank you for your comment. We agree and would like to point out that quality of life was included in the draft comprehensive research plan (Table 1).*

Comment: Are all dosage forms (e.g., transdermal, long-acting) included in the analyses?

Response: *Thank you for your comment. Yes, all dosage forms will be included as long as they are Health Canada approved and are not studied in doses which exceed specifications in the approved product monographs. This has been clarified in the comprehensive research plan.*

Comment: If combination treatment is going to be evaluated, then all potential combinations should be included to ensure consistency.

Response: *Thank you for your comments. The primary goal of this review is to examine efficacy and safety of pharmacologic treatments for OAB with the goal of informing reimbursement decisions. As such, the treatments considered for reimbursement are monotherapy. We are aware that the combination of mirabegron and solifenacin specifically may be considered for patients with tolerability limitations to higher dose antimuscarinics and that there are Phase II to IV studies of mirabegron as an add-on therapy to antimuscarinic agents. We will consider combinations only if a de novo systematic review is conducted and the comprehensive research plan has been amended to reflect this change.*

Pharmacoepidemiology Unit

Comment: The timeframes proposed for some of the analyses may not capture the most recent listings of OAB products in Ontario and other Canadian jurisdictions.

Response*: Often the data we leverage is not updated as readily as needed. Unfortunately, in the case of recently added medications such as mirabegron we will be limited due to how recently they have been added to the public formulary. We will extend*

our analysis to June 2015 to attempt to include recent medication use. Objective 3 and 4 analyses will be limited to March 2014 to allow us link to other clinical data sets (ex. Hospitalization and doctors' visits) which have not yet been updated. Dates have been changed in Objective 2.

Comment: To better reflect the complexity of treatment patterns in OAB, it is important to go beyond the duration of treatment analysis proposed and include: analyses of persistence (i.e., degree of switching amongst agents), as well as determining how many lines of therapy are required in order for patients to achieve the desired outcome.

Response: *We agree that treatment duration is only part of the important question to ask when exploring treatment patterns with OAB medications. We included exploration of persistence by reporting patients who remain on the same agents at 6 months and 1 years to help explore the percentage of patients that are adherent to OAB therapy but may have switched. We will also report which agents they switch to from the index drug as this may be of interest. We have also added additional analysis to look at the number of different agents patients use within the first year of therapy after being newly-initiated.*

Comment: Is Botox included as part of the analyses for this team?

Response*: Botox use will only be included among individuals using OAB agents. We will be reporting it among a subset of patients that are using or have used OAB agents within the time window of interest. We will only look at Botox claims that utilized the Limited Use (LU) code 440 for the indication of use of OAB.*

Comment: Are all dosage forms (e.g., transdermal, long-acting) included in the analyses?

Response: *Yes, we will explore utilization of all Health Canada approved dosage forms. This will vary by analysis based on what drugs are covered for reimbursement. For example, in Objective 1 we will be using IMS data and thus will be able to explore utilization among all payers (public and private) and will gain insight into utilization of various dosage forms paid for across Canada. In contrast, this is more limited in later objectives (2 to 4) when we explore public payer utilization, which will be limited only to products on formulary for the various provinces, and more specifically in Ontario.*

Comment: If combination treatment is going to be evaluated, then all potential combinations should be included to ensure consistency.

Response: *We will report those on combination therapy for Objective 3 separately to further explore the number and characteristics of patients who are currently on combination therapy and help gain a better understanding of the prevalence of combination use. Combination use will be defined as those with two overlapping agents that are continued for at least 2 fills. We will report the prevalence of various combinations but all combinations will*

be reported as one group in objective 3. Due to the complexity of combination therapy we will not be exploring exclude combination OAB treatment from our adherence piece in Objective 4.

Pharmacoeconomics Team

Comment: Page 3 refers to EAP listings. Note that all OAB products on the Ontario Drug Benefit Formulary are listed as LU products.

Response: *We have removed the reference to EAP.*

Comment: To make this research plan consistent with the Pharmacoepidemiology plan, persistency/adherence needs to be incorporated here as well.

Response*: We will incorporate adherence and persistency if data are available.*

Comment: There is no time horizon identified for the economic analysis; suggest using a time horizon of 1 to 5 years, to be consistent with the published literature in this therapeutic area.

Response: *We will adopt a time horizon of 1 year for the base case with 5 years in sensitivity analysis.*

Comment: Are all dosage forms (e.g., transdermal, long-acting) included in the analyses?

Response: *All OAB treatments for which clinical data from the systematic review are available will be included.*

Comment: If combination treatment is going to be evaluated, then all potential combinations should be included to ensure consistency.

Response: *All combinations for which clinical data from the systematic review are available will be included.*

Environmental Scan

Comment: **Suggest that ODPRN provide more clarity regarding which HTA bodies will be referenced as part of the international assessment.**

Response: *The HTA bodies that will be referenced include NICE, Scotland, Australia and New Zealand, as outlined under Objective 1.*

Comment: **Note that SMC is an independent entity from NICE (current wording does not reflect this separation).**

Response: *Thank you for your comment. In order to provide clarification, the study population for Scotland and NICE have been separated.*

Comment: **Are all dosage forms (e.g., transdermal, long-acting) included in the analyses?**

Response: *All dosage forms will be included (whenever information is available) as part of the analyses. This has been clarified in the Research Plan.*