Background
Healthcare resource utilization (HCRU) and associated costs are important evidence for decision-making in informing health policies for managing complex diseases such as treatment-resistant depression (TRD). TRD commonly describes major depressive disorder (MDD) in adults who respond inadequately to at least two different antidepressants of adequate dose and duration in the current depressive episode. TRD is associated with higher HCRU (psychiatrist visits, number of hospitalizations, prescriptions and neuromodulation treatments for a prolonged duration), compared to patients without TRD. HCRU estimates for TRD by the four health states (major depressive episode [MDE], remission, relapse and recovery) are limited, especially in Canada. The objective is to evaluate HCRU for the four health states of TRD, and to estimate associated costs per healthcare resource.

Methods
The Delphi method was adopted to estimate HCRU values from the perspective of the Canadian healthcare system. Two rounds of online surveys were conducted, followed by an online consensus meeting of the Delphi panel, culminating in this consensus study. The twelve panellists were:
- Experienced in treating patients with TRD
- From Alberta, British Columbia, Ontario and Quebec.
- Recruited by a third-party agency to ensure adequate blinding.
- Identified with unique codes to enable linkage of results from the surveys and to use in the consensus meeting.

Questions asked in the first-round survey were used to calculate medians which were presented in the second-round to assess panellists’ agreement. Any question which did not reach consensus were taken to the consensus meeting. The median was agreed as the value to be collected and assessed throughout the study. However, the arithmetic mean was subsequently agreed to be a more suitable measure, given that HCRU arithmetic mean estimates are often used as direct inputs for cost-effectiveness models. To accommodate for this, an average of the estimates for number of patient visits was calculated from feedback provided by the panellists, however no panellist consensus was reached on these.

Results
Ten of the 12 panellists agreed that the TRD patient treatment pathway diagram (Figure 2) was consistent with the current practice. Ten of the 12 panellists agreed that the TRD patient treatment pathway diagram (Figure 2) was consistent with the current practice.

Figure 2. Adapted patient treatment pathway for the management of patients with TRD, adapted from Kennedy et al. 2016

All panellists reported that across TRD health states, psychiatrist visits, emergency room (ER) visits (with and without hospitalization) and hospital outpatient visits were relevant in the management of patients. The study demonstrated that patients with TRD across all health states in the initial treatment setting are most likely to be prescribed selective serotonin reuptake inhibitors (SSRIs). In subsequent treatment 2 and 3 settings, patients experiencing an MDE will be prescribed with alternative SSRIS and nonphenepine reuptake inhibitors (SNRIs), and augmentation with therapies such as the antipsychotics aripiprazole and quetiapine. This treatment protocol is also reflected in patients with TRD experiencing a relapse. For patients with TRD experiencing an MDE or relapse, tricyclic antidepressants (TCADs) and monoamine oxidase inhibitors (MAOIs) are not prescribed in the initial treatment setting, with only a small proportion of patients across all health states receiving these treatments, in addition to lithium, in subsequent treatment settings. Panellists expect to treat patients with TRD experiencing an MDE or relapse for 12 weeks (the acute treatment phase) before reassessing symptoms; for relapse and recovery, it was concluded that a treatment duration of at least 52 weeks is considered for long-term maintenance treatment. Patients with TRD experiencing an MDE or relapse, on average, utilize more healthcare resources than the other health states, including:
- More physician office visits per year, most of whom will visit a primary care physician (PCP), general practitioner or family physician, or a psychiatrist.
- More use of hospital resources, including day hospital visits, hospital outpatient visits, ER visits
- 3 Require most hospitalizations, 25.8% and 17.5% of patients per year, with an estimated annual mean number of hospitalization of 0.28 ($±0.52) and 0.10 ($±0.07), and spending on average, 1.85 and 1.67 days hospital length of stay, respectively.

Figure 3. The distribution average percentage of HCRU by type of HCRU and patient health state.

Figure 3. The distribution average percentage of HCRU by type of HCRU and patient health state. Patients with TRD experiencing an MDE had the greatest costs ($14,441.81 per patient per month), followed by relapse ($3,808.57), remission ($616.85) and recovery ($129.35).

Figure 4. Mean number of visits per patient/month across different health states.

Discussion
Results from the Delphi panel study demonstrated that patients with TRD experiencing an MDE utilize a wide range of healthcare resources (e.g. psychiatrist, PCP and day hospital visits) and on average, use these healthcare resources more frequently than patients with TRD in a state of remission, relapse or recovery.

Other key findings from this Delphi panel study, in relation to the treatment choice and treatment duration, reflected the CANNAT recommended clinical guidelines.9 Panellists treat patients experiencing an MDE or relapse for eight weeks (the acute treatment phase); whereas in the health states of remission and recovery, a treatment duration for long-term maintenance treatment is at least 52 weeks. During the consensus meeting, most panellists agreed with the HCRU values presented. In instances where individual panellists did not agree, it was acknowledged that the use of healthcare resources and treatments were somewhat practice dependent. However, consensus was reached for all HCRU values based on representing the ‘average’ situation for clinical practice for Canada as a whole.

In conclusion, this study used consensus-driven methodology to determine which treatments and resources were utilized by patients with TRD, and how frequently, for each defined health state from the perspective of the Canadian healthcare system. Patients with TRD experiencing a major depressive episode or relapse were associated with higher healthcare resource utilization and constitute fewer healthcare resources and treatments. The results of this study will provide HCRU inputs to estimate the associated medical costs by health state to create awareness of the burden of disease for the TRD population in Canada.

Limitations
There are no guidelines for determining consensus, sample size and sampling techniques, which may weaken the reliability of the Delphi panel study.9 Two of the recruited panellists were unable to attend the consensus meeting, reducing the final sample size to n=10. A larger sample size could have given a more accurate reflection of Canadian clinical practice, which may have picked up additional themes relating to HCRU.

In this study, the annual median was initially agreed as the main statistical measure of central tendency in order to present the data provided by panellists. However, the monthly (defined as 28 days) mean was subsequently derived from feedback provided by the panellists and agreed to be a more suitable measure as direct inputs for cost-effectiveness analyses.

Acknowledgments:
The authors thank Ilye Fadeyi, Joshua O’Malle, Natasha Hopkins and Natasha Perry, employees of Adelphi Values, for their assistance with survey design and data collection.

References: