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Repetitive Transcranial Magnetic Stimulation (rTMS) for Treatment-resistant Depression

Health Technology Assessment

The Health Technology Assessment Unit, University of Calgary

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1 Abbreviations

APA	American Psychiatric Association
BC	British Columbia
BDI	Beck Depression Inventory
CADTH	Canadian Agency for Drugs and Technologies in Health
CAMH	Centre for Addiction and Mental Health
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBT	Cognitive behavioural therapy
CI	Confidence interval
CPR	Cardiopulmonary resuscitation
DBS	Deep brain stimulation
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive therapy
FFS	Fee-for-service
GDS	Geriatric Depression Scale
GP	General practitioner
HAM-D	Hamilton Rating Scale for Depression
HTA	Health technology assessment
iTBS	Intermittent theta burst stimulation
MADRS	Montgomery-Asberg Depression Rating Scale
MD	Medical doctor
MDD	Major depressive disorder
MST	Magnetic seizure therapy
n	Sample size
PHQ	Patient Health Questionnaire
QALY	Quality adjusted life year
QIDS-SR	Quick Inventory of Depressive Symptomatology Self-report
RR	Risk ratio
rTMS	Repetitive transcranial magnetic stimulation

SCID	Structured Clinical Interview for DSM
SNRI	Serotonin and noradrenaline reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
TBS	Theta burst stimulation
tCDS	Transcranial direct current stimulation
TRD	Treatment-resistant depression
VNS	Vagus nerve stimulation

2 Executive Summary

This report presents the findings and conclusions of a provincial health technology assessment (HTA) on implementation considerations of repetitive transcranial magnetic stimulation (rTMS) for treatment of adult treatment resistant depression (TRD). This work builds on an HTA previously completed by the University of Calgary HTA Unit, which found robust evidence of greater clinical efficacy of rTMS, with rTMS being more effective and less expensive than sham at achieving response and remission among patients with TRD. The policy question to be addressed by the present health evidence review is: 'How can rTMS be implemented in British Columbia for treatment of treatment-resistant depression, taking into account implementation considerations, patient and clinical perspectives, cost-effectiveness, and budget impact?'

The primary research questions for this HTA were:

1. What implementation models have been used for rTMS, and how could these be leveraged for the British Columbian (BC) context?
2. What are clinician and patient perspectives on implementation considerations for rTMS?
3. What is the budget impact of repetitive transcranial magnetic stimulation (rTMS) for the treatment of patients with treatment-resistant depression (TRD) in comparison to electroconvulsive therapy (ECT) and sham?

Background:

Depression is a common mood disorder that affects a person's psychological, physical, interpersonal, and occupational functioning.[1] Major depressive disorder (MDD) that does not respond to treatment is referred to as TRD and is characterized by substantial functional impairment, direct and indirect healthcare costs, and great burden for the affected individuals and their families.[2] The definition of TRD has not been standardized and ranges from failure of one antidepressant trial to failure of four or more antidepressant trials.[3] Canadian guidelines published by the Canadian Network for Mood and Anxiety Treatments (CANMAT) recommend rTMS as the first-line treatment for individuals with depression who have failed at least one trial of antidepressant treatment.[4] rTMS is a non-invasive brain stimulation technology that uses powerful and focused magnetic field pulses to induce electrical currents in specific regions of the brain.[5] The most widely accepted mechanism of the long-term antidepressant effects of rTMS is

that it alters synaptic plasticity; however, the precise mechanism of action is not yet known.[6] Electroconvulsive therapy (ECT) is recommended as second-line treatment, but may be recommended as first-line treatment in some cases, for example, acute suicidal ideation or depression with psychotic features.[4]

In 2014, the Health Technology Assessment Unit at the University of Calgary conducted an HTA of rTMS for TRD, which included a systematic review of clinical efficacy and safety and a cost-effectiveness model.[7] The systematic review found robust evidence of greater clinical efficacy of rTMS compared to sham for treatment of TRD.[7] The meta-analysis of 35 studies therein found that rTMS was twice as likely to result in response (risk ratio [RR]: 2.35 [95% confidence interval [CI]: 1.70-3.25]) compared to sham. Similarly, the meta-analysis of 18 studies therein found that rTMS was twice as likely to result in remission (RR: 2.24 [95% CI: 1.53-3.27] compared to sham. The cost-effectiveness model found that rTMS was more effective and less expensive than sham at achieving both response and remission.

Methods:

The following methodological approaches were used to gather and synthesize the available evidence:

I. Jurisdictional scan of rTMS for TRD across Canada
II. Systematic review of implementation models of rTMS
III. Clinician interviews
IV. Rapid review of patient perspectives literature
V. Implementation and budget impact analysis

Key Findings:

A survey of Canadian rTMS providers was conducted to understand the use and implementation of rTMS across Canada. Responses were received from 10 Canadian rTMS providers: four from Ontario, three from Alberta, and one each from Nova Scotia, Saskatchewan, and Quebec. rTMS was reported to be publicly funded in Alberta, Saskatchewan, and Quebec. From the four clinics surveyed in Ontario, patients were also reported to receive rTMS free of charge, with costs covered by philanthropic, hospital, or

research funds. rTMS was delivered in outpatient clinics, research studies and private clinics. It was reported that training for rTMS was provided by the Canadian rTMS distributor, by the Centre for Addictions and Mental Health, and internally by other staff trained in rTMS delivery.

A systematic review of the literature reporting on rTMS implementation models was conducted from database inception to March 2020; six relevant studies were identified. Four themes related to rTMS implementation emerged across studies, and all were discussed as important factors for treatment tolerability and success: assessment and safety, treatment room design, patient comfort, and psychoeducation. Literature described how the parameters for rTMS treatment should be determined by a psychiatrist; however, treatment could be delivered by nurses or technicians under supervision. Given the nurses' involvement in all stages of the treatment process, the creation of a trusting nurse-patient relationship was reported to have a substantial impact on the patient experience of rTMS. Studies reported enhancing treatment room comfort by adding a comfortable chair and pillows, muted wall colours, artwork featuring nature, and relaxing music. Safety precautions included hearing protection for the patients and operator, first responder training, and emergency response protocols.

Interviews were conducted with seven health care providers in BC to understand their perspectives on implementation considerations for rTMS in BC. From the interviewees' perspective, BC has a treatment gap for patients with TRD who have not responded to or are intolerant of antidepressants and for whom ECT is not an option. rTMS was perceived to be well-positioned to bridge the treatment gap for these patients, given the established body of effectiveness literature and relative ease of administration. Health care providers perceived rTMS to be cheaper than ECT, and all agreed that there was patient demand for rTMS as an alternative treatment option to medications and/or ECT. Access to rTMS in BC was reported to be inequitable, as it is currently only offered in a few clinics in Victoria and the Vancouver region. Current access was perceived to be further limited by the high cost of treatment, the need to pay for accommodations out-of-pocket, and the time commitment associated with daily treatment administration for working individuals. Health care providers discussed several models of

implementation of rTMS into the BC health system, which included community clinics or in-hospital administration, stressing that both options are associated with corresponding benefits and drawbacks.

A rapid review of the qualitative literature on patient and caregiver perspectives on rTMS was conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH). One study met the inclusion criteria and was included in the CADTH report. It explored the reasons for self-referral for rTMS among 98 individuals. Six key reasons were identified: current treatment not working; proactively seeking information about treatment for depression; suffering from chronic or long-term depression; desperate for relief from depression; motivated to seek alternative treatment owing to side-effects of current or previous treatment; and getting worse in spite of the current treatment regime. The included study concluded that the reasons for self-referral were heterogeneous, revealing that rTMS had broad appeal across age groups and for various reasons. This rapid review highlights a gap in patient perspective literature.

Based on the evidence presented herein, three implementation scenarios for the provision of rTMS for patients with TRD were explored: 1) maintain status quo where rTMS is not publicly funded, 2) the province pays for and delivers all components of rTMS, 3) a community-delivered model in which rTMS providers are paid by fee for service or capitation. Each has unique advantages and disadvantages including impact on health and non-health benefits, provincial expenditure, and access equity. A budget impact analysis was conducted over a 3-year time horizon and based on an eligible cohort of 11,088 patients to estimate costs associated with rTMS provision in BC based on the above scenarios (Table 1). [redacted]

Table 1. Estimated Budget Impact over Three Years

	Predicted Budget Impact			
	Year 1	**Year 2**	**Year 3**	**Total**
Scenario 1: Status quo • rTMS is not publicly funded by the province.	$0	$0	$0	$0
Scenario 2: Provincial funding and delivery of rTMS funded by the province.	$7,317,516	$7,317,516	$7,317,516	$21,952,548
Scenario 3: Provincial funding with community private delivery of rTMS.	$7,317,858	$7,317,858	$7,317,858	$21,953,575

*FFS paid per patient per week is $33.90; Capitation fee paid per patient per month is $34.90.

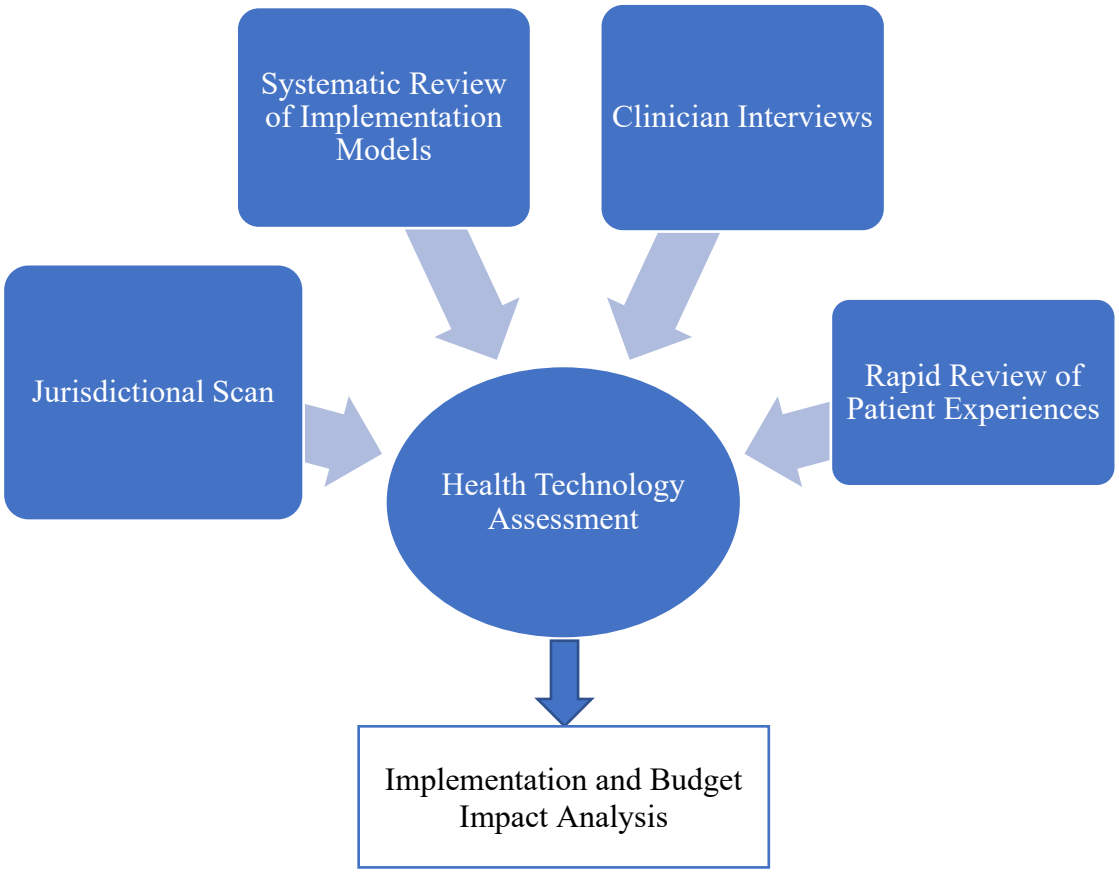
Conclusions:

Broadly, the evidence presented in this HTA describes how rTMS has considerable health advantages for treatment of TRD and few disadvantages. Interviewed BC health care providers describe how rTMS fills a treatment gap for patients who have not responded to or are intolerant of antidepressants and for whom ECT is not an option. All seven health care providers unanimously feel that rTMS should be publicly funded for people with TRD, considering the impact rTMS has on a patient's daily functioning, quality of life, and ability to work. rTMS is publicly funded in Alberta, Saskatchewan, and Quebec, and generally provided for free in Ontario, with costs covered by philanthropic, hospital, or research funds. Public funding across these four Canadian provinces is aligned with current Canadian guidelines recommending that rTMS be used as a first-line treatment for depression after failing at least one trial of antidepressants. Considerations for rTMS implementation in BC include patient comfort during treatment delivery; recruitment, roles, and responsibilities of rTMS technicians and supervising psychiatrists; equitable access; and patient barriers to access (e.g. potential cost to patients who relocate to receive treatment).

3 Purpose of this Health Technology Assessment

The purpose of this health technology assessment (HTA) is to synthesize the evidence on the implementation considerations of repetitive transcranial magnetic stimulation (rTMS) for treatment of adult treatment-resistant depression (TRD). This report builds on an HTA previously completed by the University of Calgary HTA Unit, which found robust evidence of greater clinical efficacy of rTMS when compared to sham for treatment of TRD for response and remission. In addition, the previous work found rTMS to be more effective and less expensive than sham at achieving response and remission. The present report focuses on implementation of rTMS in British Columbia (BC). It summarizes the current context on the use of rTMS for depression in BC and Canada, presents a rapid qualitative review of patient perspectives, and synthesizes the available literature on rTMS implementation models. Finally, an implementation and budget impact analysis are presented with a range of implementation scenarios, each with unique advantages and disadvantages including impact on health and non-health benefits, provincial expenditure, and access equity (Figure 1).

Figure 1. Summary of Process



4 Research Question and Objectives

The primary research questions for this health technology assessment (HTA) were:

1. What implementation models have been used for repetitive transcranial magnetic stimulation (rTMS), and how could these be leveraged for the British Columbian (BC) context?
2. What are clinician and patient perspectives on implementation considerations for rTMS?
3. What is the budget impact of rTMS for the treatment of adult patients with treatment-resistant depression (TRD) in comparison to electroconvulsive therapy (ECT) and sham?

A variety of methodological approaches were used to gather and synthesize the available evidence in order to address the primary research question. The following methodologies were used:

I. Jurisdictional scan of rTMS for depression across Canada
II. Systematic review of implementation models of rTMS
III. Clinician interviews
IV. Rapid review of patient perspectives literature
V. Implementation and budget impact analysis

5 Background

5.1 Overview of Depression

5.1.1 Symptoms and Prevalence of Depression

Depression is a common mood disorder that affects a person's psychological, physical, interpersonal, and occupational functioning.[1] Psychological symptoms of depression include depressed mood (e.g., feelings of sadness, hopelessness, or irritability), disinterest in pleasurable activities, disturbances to cognitive functioning (e.g., difficulty concentrating), feelings of worthlessness and guilt, and thoughts of suicide.[1] Physical symptoms of depression include significant weight gain or loss when not dieting, sleep disturbances (e.g., insomnia), fatigue, and psychomotor agitation/retardation.[1]

Major depressive disorder (MDD) is the most common mood disorder included in the Depressive Disorders section of the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5).[1] Other depressive disorders include persistent depressive disorder (dysthymia), disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. Depression also occurs as part of bipolar disorders (Bipolar and Related Disorders in the DSM-5), which are characterized by alternating manic and depressive mood episodes.[1]

Depression affects more than 264 million people worldwide.[8] It is a leading cause of disability and contributes greatly to the global burden of disease.[8] In 2012, 11.3% of the Canadian population aged 15 and over reported a lifetime prevalence of a major depressive episode, with 4.7% of the population experiencing it over the past 12 months.[9] These rates were similar to the rates of a major depressive episode reported in BC in 2012, which consisted of a lifetime prevalence of 11.6% and a 12-month prevalence of 4.6%.[9] Depression affects more women than men; compared to women, men are more likely to present with symptoms of irritability, discouragement and anger.[10] Individuals who experience one episode of depression are 50% more likely to experience additional episodes throughout their lifetime.[10]

5.1.2 Diagnosis of Depression

A clinical diagnosis of depression can be made by a psychiatrist, a psychologist, or a general practitioner. To meet diagnostic criteria for a major depressive episode in the DSM-5, an individual has to exhibit at least five symptoms of depression for at least two weeks, the symptoms must affect the individual's ability to function, and not be due to physiological effects of a substance or another medical condition (Table 2).[1] The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide that can be used to make DSM diagnoses.[11]

Table 2. Summary of MDD Criteria in the DSM-5

Criteria	Symptoms
A	Five (or more): of the following symptoms over the past two weeks, representing a change from normal functioning: 1. depressed mood, 2. diminished interest/pleasure, 3. significant weight gain/loss when not dieting, 4. insomnia/hypersomnia, 5. psychomotor agitation/retardation, 6. fatigue/energy loss, 7. feelings of worthlessness or inappropriate guilt, 8. diminished concentration/ability to think, 9. recurrent thoughts of death or suicide
B	Symptoms cause significant distress or impairment (e.g., social or occupational)
C	Not attributable to physiological effects of a substance or another medical condition

Source: American Psychiatric Association, 2013[1]

Several validated clinician-administered and self-rating tools may be used to assess whether an individual is experiencing symptoms of depression. Used alone, these measures cannot diagnose depression; however, they may be used as a screening tool prior to a formal diagnosis process.

These tools are also frequently used for monitoring treatment progress and in psychotherapy research. Widely used clinician-administered tools include the Hamilton Rating Scale for Depression (HAM-D)[12] and the Montgomery-Asberg Depression Rating Scale (MADRS).[13] Commonly used self-rating tools include the Beck Depression Inventory II (BDI-II),[14] the Quick Inventory of Depressive Symptomatology Self-report (QIDS-SR),[15] the Geriatric Depression Scale (GDS),[16] and the Patient Health Questionnaire (PHQ-2 and PHQ-9).[17,18]

Depression, and mood disorders, are underdiagnosed and underrecognized.[19] Individuals experiencing symptoms of depression may not seek treatment due to low mental health literacy, fear of stigmatization, or wanting to manage their own mental health.[19] Health system factors contributing to underdiagnosis of depression include access to services and limited knowledge and skills of the healthcare providers who are consulted.[19] Most individuals with mood disorders seek treatment in primary care, where these disorders remain particularly unrecognized;[20] only 50% of individuals with depression who seek treatment from primary care providers receive an accurate diagnosis.[19]

5.1.3 Risk Factors for Depression

There is no single cause of depression, and it is postulated that depression may be caused by an interplay of genetic and environmental risk factors,[21] exposure to which changes throughout the lifespan.[22] Some risk factors for depression include:[10,23]

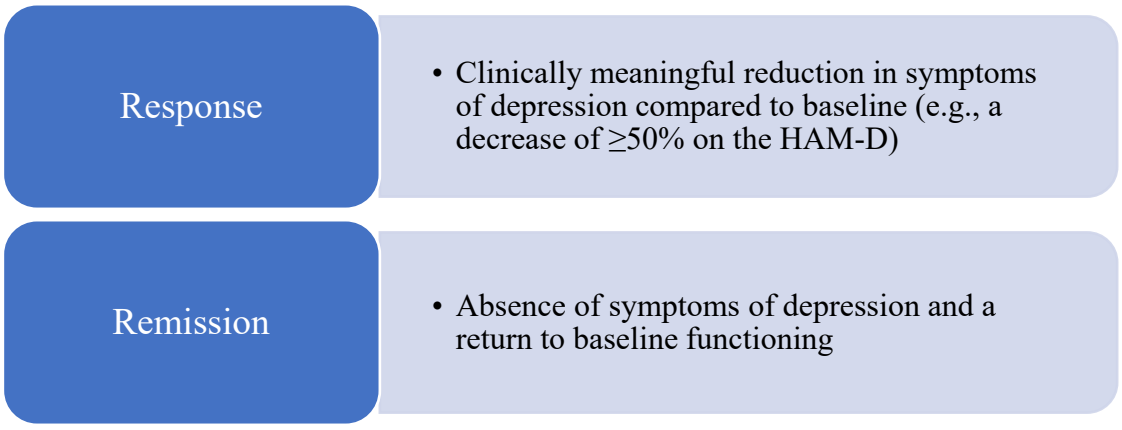
- genetic or family history of depression
- psychological or emotional vulnerability to depression, including certain personality traits (e.g., low self-esteem)
- biological factors (e.g., imbalances in brain chemistry and in the endocrine/immune systems)
- traumatic or stressful life events (e.g., abuse)
- being lesbian, gay, bisexual or transgender, or having variations in the development of genital organs that are not clearly male or female (intersex) in an unsupportive situation
- history of other mental health disorders (e.g., anxiety disorders)
- abuse of alcohol or recreational drugs

- serious or chronic illness (e.g., cancer)
- certain medications (e.g., some high blood pressure medications or sleeping pills).

5.1.4 Canadian CANMAT Guidelines for Treating MDD

Treatments for depression include psychological (e.g., cognitive behavioural therapy [CBT]) and pharmacological (e.g., selective serotonin reuptake inhibitors [SSRIs]) treatments.[8] Different treatments may be more appropriate for treating depression in the "acute" versus "maintenance" stage. The objective of acute treatment is alleviating current symptoms of depression to achieve response and remission and return to full functioning, whereas maintenance treatment focuses on prevention of relapse and recurrence.[24] Response refers to a clinically meaningful reduction in symptoms of depression compared to baseline (e.g., a decrease of ≥50% on the HAM-D);[25] remission refers to the absence of symptoms of depression and a return to baseline functioning (Figure 2).[26]

Figure 2. Definitions of Response and Remission



The 2016 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines recommend psychoeducation, self-management, and psychological treatment for individuals with depression of mild severity; however, pharmacological treatments may be considered depending on patient preference.[27] CANMAT recommends CBT as the first-line psychotherapy treatment for both acute and maintenance treatments of MDD.[28] Interpersonal therapy or behavioural activation are both recommended as first-line acute treatments and second-line maintenance treatments.[28] For individuals with moderate-to-severe depression, a combination of

psychotherapy treatment and antidepressant medication is recommended.[28] First-line pharmacological treatments recommended by CANMAT primarily include SSRIs (e.g., citalopram) and serotonin and noradrenaline reuptake inhibitors (SNRIs; e.g., duloxetine).[27]

Neurostimulation or neuromodulation treatments for treatment of depression include rTMS, transcranial direct current stimulation (tDCS), ECT, and magnetic seizure therapy (MST); invasive surgical techniques for treatment of depression include vagus nerve stimulation (VNS) and deep brain stimulation (DBS).[4] CANMAT recommends rTMS as the first-line treatment for individuals with depression who have failed at least one trial of antidepressant treatment (a more detailed description of rTMS is reported in Section 1.2).[4] ECT is recommended as second-line treatment, but may be recommended as first-line treatment in some cases, for example acute suicidal ideation or depression with psychotic features.[4]

CANMAT notes that rTMS and ECT should be viewed as complementary treatments, rather than competing, given their differences in mechanisms, tolerability, and acceptability.[4] The evidence examined by CANMAT suggests that ECT is superior to rTMS with respect to response and remission, and patients for whom ECT has failed have poor response rates to rTMS. Therefore, CANMAT suggests that rTMS be pursued prior to attempting ECT, and that patients for whom ECT has not been effective are unlikely to respond to rTMS. Although treatment-resistant depression (TRD) is one of the situations in which CANMAT suggests that ECT may be warranted as first-line treatment over rTMS, no specific recommendations are provided regarding how to choose which treatment may be more appropriate.[4]

5.1.5 Treatment Challenges

Depression remains largely undertreated. A recent study conducted with population-level data in British Columbia in 2016 found that only 53% of individuals diagnosed with MDD received minimally adequate treatment (defined as either antidepressant treatment filled with a supply of ≥84 days or receipt of ≥4 psychotherapy/counselling sessions).[29] Less than half of the individuals (48%) received minimally adequate treatment in the form of antidepressants only, and only 13% received minimally adequate psychotherapy/counselling treatment.[29] Another study of British Columbians found that 92% of individuals seeking treatment for depression only received care

from their primary care provider without any specialist support (e.g., referral to a psychiatrist).[30] Although psychological treatments (e.g., CBT) are also recommended by the CANMAT guidelines, they are can be expensive and time-consuming, which makes them less accessible to the general population, given that these treatments are often not funded by the medical services plan (MSP).

Among individuals that do receive adequate treatment for depression, less than 50% respond to first-line treatment of psychotherapy or antidepressants.[2] MDD that does not respond to treatment is referred to as TRD and is characterized by substantial functional impairment, direct and indirect healthcare costs, and great burden for the affected individuals and their families.[2] Risk factors for TRD include severity and chronicity of the illness, presence of a comorbid psychiatric or medical condition, and older age.[31] It is estimated that >50% of patients with MDD have a comorbid psychiatric, personality, or medical condition; the presence of these comorbid conditions is believed to be related to a decreased treatment response.[31] In a study examining the effectiveness of CBT for inpatients with TRD (defined as at least two failed trials of antidepressants), the following comorbidities were the most common: generalized anxiety disorder (72.4%), social phobia (60.3%), agoraphobia (51.3%), dysthymia (36.5%), and post-traumatic stress disorder (32.7%).[32]

The definition of TRD has not been standardized and ranges in the literature from failure of one antidepressant trial to failure of four or more antidepressant trials.[3] In Canada, CANMAT refers to TRD as failure of at least one or two antidepressant trials but notes that this definition has not been standardized; therefore, the degree of resistance (e.g., failure of at least one antidepressant trial) is specified throughout the CANMAT guidelines whenever possible.[4] In the United Kingdom, the National Institute for Health and Care Excellence (NICE) defines TRD as a lack of response to two antidepressants.[33] Despite there being differences in definitions, in a clinical sense, TRD is conceptualized as depression where the person is unable to return to their usual activities despite courses of treatment.[34] Although several models for staging TRD have been proposed, no one model is widely accepted.[35]

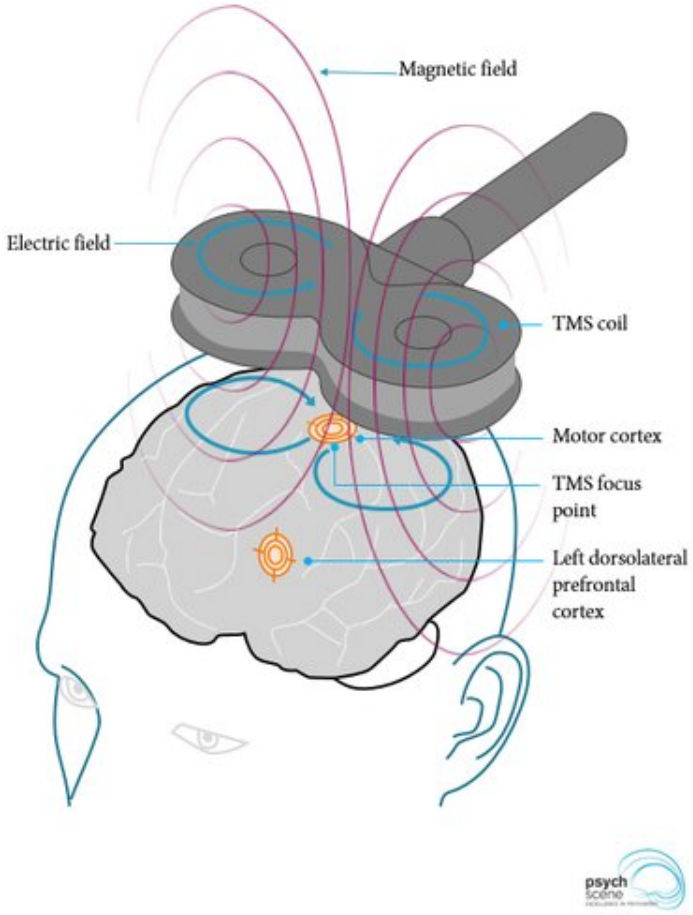
A Canadian chart review study examining the prevalence of TRD (defined as failure of at least two antidepressant trials in patients seeking treatment for depression) across Canada found a rate of 21.7% in 2008-2009.[36] BC had the highest prevalence rate of TRD (28%), compared to Ontario (24%), Manitoba (22%), Quebec (13%), the Atlantic Provinces (15%), and Alberta (12%).[36] Across Canada, patients with TRD were significantly more likely to have comorbid mental health conditions (primarily anxiety and substance use disorders), personality disorders (primarily in the anxious-fearful cluster), and medical conditions (primarily cardiovascular disease, chronic pain, and sleep disorders) compared to their non-TRD counterparts.[36]

5.2 Repetitive Transcranial Magnetic Stimulation

5.2.1 rTMS Overview

rTMS is a non-invasive brain stimulation technology that uses powerful and focused magnetic field pulses to induce electrical currents in specific regions of the brain.[5] It is administered by a trained technician or a nurse, under supervision of a physician or a psychiatrist. Unlike ECT, it does not induce a seizure and does not require anesthesia.[4] The process involves placing a plastic-encased electromagnetic coil against the patient's scalp and using a high-current pulse generator to create an electric current to flow through the coil and create a magnetic field (Figure 3).[37] Treatment is typically administered with the patient sitting down in a reclined position. The most widely accepted mechanism of the long-term antidepressant effects of rTMS is that it alters synaptic plasticity; however, the precise mechanism of action is not yet known.[6] Convergent findings across multiple studies of the therapeutic effects of rTMS suggest that it broadly alters neurophysiological and neurochemical parameters, such as blood flow and activity in brain regions involved in depression.[38]

Figure 3. Illustration of rTMS Technology



Source: Psych Scene Hub, 2020[39]

Standard protocols involve delivering rTMS once per day, five days a week, for a duration of up to four weeks; however, the frequency and number of sessions may be amended depending on individual patient needs.[4] Treatment protocols vary with respect to variability in intensity, frequency, and stimulation site, which may all exert different effects. A typical rTMS session delivered at 10 Hz lasts for 37.5 minutes; however, emerging evidence suggests that the session time can be reduced to 3 minutes with intermittent theta burst stimulation (iTBS), a newer form of rTMS.[40] iTBS was approved by the Food and Drug Administration for treatment of TRD in August of 2018.[41]

Health Canada approved rTMS for treatment of depression in Canada in 2002;[5] however, rTMS

is currently only publicly funded in Alberta, Saskatchewan, and Quebec.[42] First-line rTMS protocols for treatment of acute TRD recommended by CANMAT are either high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) or low-frequency rTMS to the right DLPFC.[4] Although maintenance rTMS for TRD appears to be promising, CANMAT does not yet have sufficient evidence to make any recommendations regarding specific maintenance protocols.[4]

5.2.2 Contraindications for use of rTMS

rTMS is generally contraindicated for patients with a history of epilepsy or seizures.[5] Absolute contraindications to rTMS include the presence of ferromagnetic or magnetic sensitive metal hardware implanted in the head and neck, such as aneurysm clips, cranial implants, brain stimulators, or electrodes, as well as implanted cardiac defibrillators and pacemakers.[5,43] A thorough patient evaluation should be conducted prior to commencing treatment to assess whether the patient has been exposed to any metal piercings or tattoos with ferromagnetic ink in the head and neck region.[33] Any non-ferromagnetic orthodontic hardware, such as braces or fillings, is considered safe.[33]

5.2.3 Clinical Efficacy of rTMS

There is substantial literature published on the clinical efficacy of rTMS. In 2014, the Health Technology Assessment Unit at the University of Calgary conducted a HTA of rTMS for TRD, which included a systematic review of clinical efficacy and safety.[7] The systematic review identified 70 relevant RCTs, which included the following comparator pairs: rTMS versus sham (n=45); high- versus low-frequency rTMS (n=14); standard rTMS versus other rTMS protocols (n=13); rTMS versus ECT (n=6); unilateral versus bilateral rTMS (n=5); and high- versus low-intensity rTMS (n=3). The studies were generally assessed to be of moderate quality, with most having a combination of unclear and low risks of bias, and few having high risks of bias.[44] The majority of the included studies were conducted in the United States, and Australia, with very few studies conducted in Canada. However, the findings were considered to be generalizable to the Canadian context, given that the patient mix and underlying etiology of MDD and TRD are likely comparable across these countries.[7]

The 2014 systematic review found robust evidence of superiority of rTMS compared to sham for treatment of TRD.[7] A meta-analysis of 35 studies found that rTMS was twice as likely to result in response (risk ratio [RR]: 2.35 [95% confidence interval [CI]: 1.70-3.25]) compared to sham (Table 3). Similarly, a meta-analysis of 18 studies found that rTMS was twice as likely to result in remission (RR: 2.24 [95% CI: 1.53-3.27] compared to sham. An optimal rTMS treatment protocol did not emerge because meta-analyses did not identify any statistically significant differences in response and remission rates between high- and low-frequency, unilateral and bilateral, and high- and low- intensity rTMS protocols. Lastly, a meta-analysis of three studies found that rTMS was not statistically different from ECT with respect to achieving response (RR: 1.09 [95% CI: 0.79-1.48]) and remission (RR: 0.97 [95% CI: 0.65-1.45].[7]

Table 3. Summary of 2014 Meta-analysis Results, All Random Effects

	Outcome	Number of studies pooled	Pooled Risk Ratio (95% CI)	I^2	p
rTMS versus sham	Response	31	2.35 (1.70-3.25)	36.1%	0.025
	Remission	18	2.24 (1.53-3.27)	1.1%	0.441
rTMS versus ECT	Response	3	1.09 (0.79-1.48)	0.0%	0.416
	Remission	3	0.97 (0.65-1.45)	0.0%	0.873

A recent network meta-analysis examining eight different rTMS interventions compared to sham for acute depression found that most interventions were superior to sham with respect to response and remission.[45] Notably, priming rTMS, bilateral rTMS, high-frequency rTMS, TBS, and low-frequency rTMS, were all found to be superior to sham with respect to response. Priming rTMS, bilateral rTMS, high-frequency rTMS, and low-frequency rTMS, were all found to be superior to sham with respect to remission. Although the network meta-analysis was not specific to TRD, 74.1% of the studies included in the network included TRD patients only.[45]

5.2.4 Safety of rTMS

A systematic review of safety was conducted by the Health Technology Assessment Unit at the University of Calgary as part of the HTA on rTMS for TRD.[7] The most frequently reported adverse effects in the 45 studies assessing rTMS versus sham were pain/discomfort and headache. Ten studies reported that some of their patients had headaches, all of which subsided

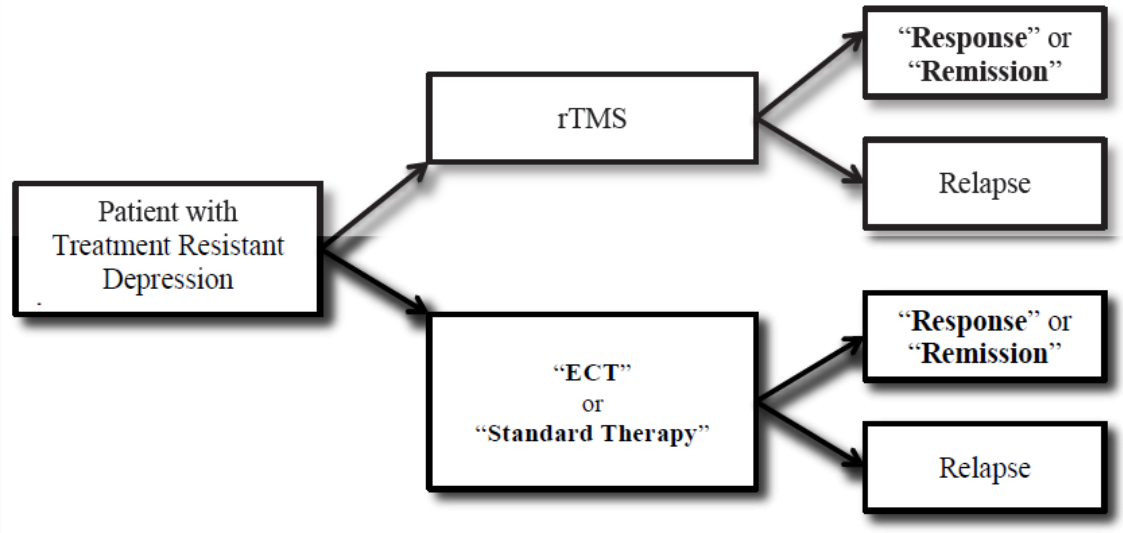
quickly. Headaches occurred both in the sham and rTMS groups but were slightly more common in the rTMS group (up to 60% for rTMS versus up to 50% for sham). Nine studies reported rates of patient discomfort or pain. In six of these studies, discomfort and pain were reported in both the rTMS and sham groups; the remaining three studies reported only pain/discomfort in the rTMS group. None of the included studies comparing rTMS to sham assessed serious adverse events, such as cognitive impairment, seizures, or suicide ideation.

The only adverse effects reported in the six included studies assessing rTMS versus ECT were pain/discomfort and headache. Three studies reported that some of their patients had headaches, all of which subsided quickly. Only one study reported rates of patient pain/discomfort: six participants in the rTMS arm reported pain and/or discomfort, and no patients in the ECT group reported pain or discomfort. None of the included studies comparing rTMS to ECT reported serious adverse events, such as cognitive impairment or seizure.

5.2.5 Cost-effectiveness of rTMS

A cost-effectiveness analysis was conducted by the HTA Unit at the University of Calgary in 2014, as part of the health technology assessment of rTMS for TRD.[7] The cost-effectiveness model was a simple decision model comparing rTMS to standard therapy (sham) and ECT across three health states: response, remission, and relapse. Given that no long-term data on relapse were available from the systematic review of clinical efficacy, the model only considered response and remission. Only the costs of therapy were included in the model (Table 4). Cost of standard therapy was based on the average cost of generic versions of three separate SSRIs (Citalopram, Paroxetine, and Fluoxetine) given as standard dosage for two treatment courses, given that "two failed treatment courses of six weeks duration" is the general definition of TRD.[46] The cost of one course of ECT was developed from a description of what is typically done in centers within Alberta, specifically the Centennial Centre in Ponoka, AB, accounting for the staff involved, cost of the machine and disposable tools, and amortization rate. The cost of one course of rTMS was developed using the machine costs provided by the Riverview Centre in Calgary, AB, accounting for the staff involved, cost of the machine and import fee, and amortization rate.

Figure 4. 2014 Cost-effectiveness Model Overview



Source: HTA Unit, 2014[7]

Table 4. Cost Inputs for Each Individual Treatment Course for 2014 Cost-effectiveness Model

	Cost (CAD)	Description	References
Standard Therapy	45$	Citalopram ($0.2397 per 20 or 40mg pill), Paroxetine ($0.4513 per 20mg pill), and Fluoxetine ($0.4598 per 20mg pill) costs averaged at 1 pill per day for two 6-week periods	Drugs.com, AIDBL
ECT	3,324$	Nurse at $45.03 per hour for an hour, Anesthesiologist $107.27 per session, and Psychiatrist $84.73 per session. Machine costs $70,000 over 10 years with an average of 500 sessions per year, and $13,000 in disposable airway tools per year. Estimated for initial 12 sessions of treatment.	SOMB Price List, AHS Job Board, Centennial Centre (Ponoka)
rTMS	952$	Nurse at $45.03 per hour for half an hour per session and Psychiatrist $84.73 for first session only. Machine costs $80,000 (extra $5,000 import fees), over 10 years with an average of 408 sessions per year. Estimated for initial 20 sessions of treatment.	SOMB Price List, AHS Job Board, Riverview Centre (Calgary)

Abbreviations: AHS: Alberta Health Services; AIDBL: Alberta Interactive Drug Benefit List; SOMB: Schedule of Medical Benefits

The cost-effectiveness analysis found that rTMS was more costly and more effective than sham at achieving response and remission with a cost per quality adjusted life year (QALY) gained of $13,084 and $20,203, respectively.[7] When comparing rTMS to ECT, rTMS is less expensive and more effective than ECT at achieving response, and also less expensive and more effective at achieving remission (ECT has a cost per QALY gained of $328,325 compared to rTMS).[7]

5.2.6 Emerging rTMS Technologies

An important consideration in the field of rTMS for TRD is the recent research examining the accelerated iTBS protocol, which consists of delivering 10 treatment sessions per day for five consecutive days.[47] Preliminary findings suggest that this accelerated iTBS protocol is well-tolerated and safe; however, larger, sham-controlled RCTs are necessary to confirm these findings.[47] One such study is currently underway by CAMH in collaboration with the UBC Hospital.[48] Confirmation of the preliminary findings in this larger study may help to position iTBS as a cheaper and safer alternative to ECT. The shorter duration protocol (five days versus the traditional four-to-six weeks protocol) would make the need for temporary relocation much easier for patients not living within driving distance to a treatment centre, thereby decreasing a major barrier to access.

6 Jurisdictional Scan of rTMS Implementation for Depression across Canada

Summary

- rTMS is publicly funded for the treatment of depression in Alberta (public funding and delivery), Quebec (public funding and community delivery), and Saskatchewan (funding model not reported).
- Ten Canadian rTMS providers from Alberta (n=3), Nova Scotia (n=1), Ontario (n=4), Saskatchewan (n=1), and Quebec (n=1) were surveyed about rTMS treatment for depression in their clinic/province.
- Across Canada, rTMS was reported to be delivered in outpatient clinics, research studies, and private clinics.
- Across the Ontario clinics surveyed, patients were reported to receive rTMS free of charge, with the cost covered by philanthropic, hospital, or research funds.
- rTMS was reported to be primarily delivered by technicians or nurses, under the supervision of physicians (psychiatrists).
- Training to rTMS providers was reported to be provided by the Canadian rTMS distributor, a course developed at the Centre for Addiction and Mental Health (CAMH), and internally by rTMS-trained staff.
- Additional supports (e.g., help finding low-cost accommodation) were generally not reported to be provided to patients undergoing rTMS in a clinical context; some support (e.g., help with transit tickets, parking) was reported to be provided to patients in some rTMS research studies.

6.1 Purpose

To understand how rTMS has been implemented for treatment of depression in clinics across Canada.

6.2 Methods

A survey was developed and circulated to Canadian rTMS providers via email. The purpose of the survey was to understand implementation of rTMS for treatment resistant depression in each jurisdiction. Survey questions pertained to the settings in which rTMS is offered; clinic staffing model and rTMS training provided to the technicians; number of machines in the clinic; the number of patients treated annually; cost of rTMS; and any additional assistance provided to the patients (e.g., financial). Full survey questions are available in Appendix A.

An attempt was made to locate contact information for at least one rTMS provider from each province and territory, except for British Columbia. In-depth interviews were conducted with British Columbian clinicians and a detailed description of current practice in this province can be found in Section 8.

6.3 Results

The survey was sent to 22 Canadian rTMS providers. Responses were received from ten providers across five provinces: Alberta (n=3), Nova Scotia (n=1), Ontario (n=4), Saskatchewan (n=1), and Quebec (n=1). Nine of the responders were psychiatrists, and one respondent was an academic researcher. A summary of providers' responses is reported in Table 5.

In Canada, rTMS for treatment of depression is publicly funded in Alberta (since 2019), Saskatchewan (since 2013), and Quebec (since 2013) (Figure 5). Data on the number of publicly funded rTMS treatments performed annually in these provinces were not publicly available.

Figure 5. Public Funding for rTMS across Canada

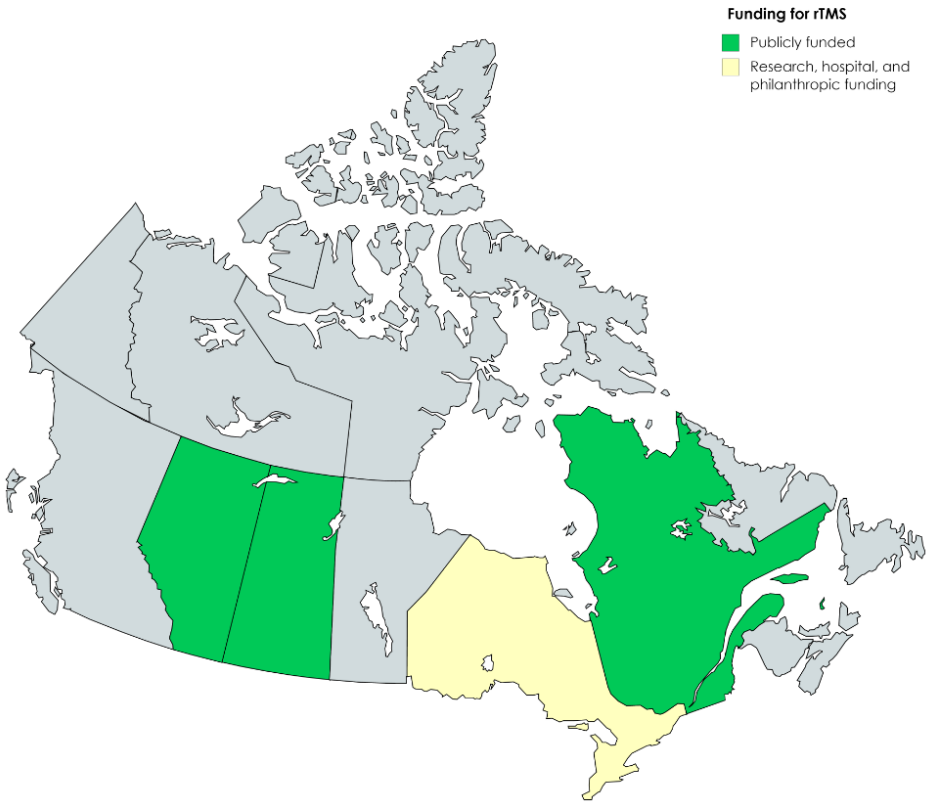


Table 5. Summary of Survey Responses from Canadian rTMS Providers

Settings	• Outpatient clinics (within acute care or psychiatry offices) • Private clinics • Within research studies
Staff Roles and Responsibilities	**Psychiatrists:** • Perform assessment • Determine motor threshold and treatment parameters • Provide psychoeducation • Supervise patient care, monitor treatment and follow-up
	Technicians: • Deliver treatment
Training	• Vendor training • Internal/external training by a psychiatrist with rTMS experience • On-site orientation • CAMH course • Basic regional courses for certification • Training and accreditation from the University of Toronto
Types of Machines	• MagVenture MagPro R30 with cooling system with theta burst option • MagVenture R20 • Brainsway
Number of Patients Treated per Year per Clinic (Range)	• 20 to 700
Patient Assistance	• Funding for active servicemen provided through the Forces • Parking or transit cost covered if in research study • Some patients apply for a general Ontario program that supports travel costs
Cost of the rTMS Service to Patients	• No cost in publicly funded facilities in jurisdictions where rTMS is funded • No cost in research studies • No cost in select clinical settings in jurisdictions where rTMS is not funded • Out-of-pocket in private clinics

Abbreviations: CAMH: The Centre for Addiction and Mental Health; rTMS: repetitive transcranial magnetic stimulation

6.3.1 rTMS Implementation

6.3.1.1 Alberta

Three Alberta rTMS providers responded to the survey. It was reported that rTMS in Alberta is administered through outpatient programs at acute care sites where it is publicly funded and delivered by Alberta Health Services, private clinics for which patients pay out-of-pocket, and research studies where the cost is borne by the researchers. There are 12 publicly funded MagPro R30 rTMS machines in Alberta that were used to treat approximately 128 new patients and 16 maintenance patients in 2019.

Publicly funded rTMS treatment in Alberta was reported to be delivered by technicians under the supervision of a licensed rTMS-trained physician (psychiatrist); it was reported that a registered nurse is present for patient assessments and medical care. Technicians delivering rTMS were reported to have received training that included training delivered by an rTMS vendor; training by an internal/external psychiatrist with rTMS experience; and on-site orientation. No financial assistance (e.g., accommodation or transportation costs) was reported to be provided to the patients. It was also noted that Alberta strives to have a province-wide rTMS program with devices in satellite clinics, which would necessitate a province-wide referral and triage system.

6.3.1.2 Saskatchewan

One Saskatchewan rTMS provider responded to the survey. rTMS was reported to be administered in an outpatient psychiatry office and to be funded by Saskatchewan health insurance; information on the provincial funding model was not reported. The respondent reported having two MagVenture rTMS machines but stated that one machine was adequate. The clinic was reported be using iTBS to treat 15-22 patients per day (including maintenance patients), with numbers sometimes going up to 25-30 patients per day.

It was reported that rTMS treatment in the clinic was delivered by one LPN who was trained by Roxon (distributer of MagVenture in Canada) and the supervising psychiatrist. It was noted that the supervising psychiatrist conducts psychoeducation before starting treatment (e.g., discussion of possible side effects, showing an educational video) and reviews the patients pre-treatment, during treatment, and near the end, with monitoring increased if adverse effects are present. The

psychiatrist was also reported to conduct treatment follow-up and maintenance. No financial assistance (e.g., accommodation or transportation costs) was reported to be provided to the patients.

6.3.1.3 Ontario

Four Ontario rTMS providers responded to the survey. rTMS was reported to be administered in Ontario through outpatient clinical care and research studies. Although rTMS is not publicly funded in Ontario, all respondents indicated that there is no cost to patients receiving rTMS at their clinics; the cost is covered through philanthropic, hospital, and/or research funds. Across clinics, the number of unique patients treated annually ranged from 67 to 700 per clinic, including new and maintenance patients. The number of machines across clinics ranged from one to seven, with MagVenture devices being the most common.

rTMS was generally delivered by trained rTMS technicians; one clinic reported having registered nurses deliver the treatments. It was reported that the role of physicians (psychiatrists) includes ordering treatments, determining motor threshold and stimulation parameters, and overseeing treatment (including making decisions about whether to continue or stop treatment). It was reported that training was provided through a course at the Centre for Addiction and Mental Health (CAMH) and internal on-site training to new staff provided by trained nurses and psychiatrists. Some respondents indicated that they help to cover the cost of transit tickets and parking for patients receiving rTMS as part of a research study. One respondent noted that some patients apply for a more general Ontario program that exists to support travel costs for patients needing to travel to hospital for treatments or assessments. No other financial assistance (e.g., accommodation costs) to patients was reported.

6.3.1.4 Quebec

One Quebec rTMS provider responded to the survey. It was reported that rTMS in Quebec is administered through adult psychiatric outpatient clinics where it is publicly funded and community delivered (i.e., fee-for-service) and through private clinics in the community. Clinicians can only bill for rTMS if it is done in a hospital setting, in which case it is administered at no cost to patients. The clinic, which is located in a hospital setting, was reported

to have four machines, of which three are in use (MagVenture MagPro R30 with theta burst option). In 2018, the clinic was reported to have administered a total of 4,045 treatments, across 67 new patients and 25 maintenance patients.

Staffing was reported to differ across clinics. It was reported that this clinic is staffed by an on-site physician and a technician in electrophysiology who assists with pre-treatment assessment (e.g., determining motor threshold) and assists in the clinic. rTMS courses for technicians and nurses were reported to be regionally offered in Montreal and Toronto. No financial assistance (e.g., accommodation or transportation costs) was reported to be provided to the patients by the clinic. The respondent also noted that they strive to make rTMS available in many regions so that patients can be treated locally, but that the uptake has been slow.

6.3.1.5 Nova Scotia

One Nova Scotia rTMS provider responded to the survey. rTMS was reported to be administered in a private clinic where patients are required to pay for the treatment out-of-pocket (treatment cost was not reported). The respondent noted that the clinic has one MagVenture R20 machine and treats about 20-24 patients per year. rTMS treatment in the clinic was reported to be delivered primarily by a psychiatric nurse who was trained and accredited by the University of Toronto. Psychiatrists were reported to be responsible for screening and monitoring patients throughout treatment. It was noted that patients who are active servicemen receive funding through the Forces; otherwise, no financial assistance (e.g., accommodation or transportation costs) was reported to be provided to the patients by the province.

6.4 Conclusions

rTMS is publicly funded for the treatment of depression in Alberta, Saskatchewan, and Quebec. In Alberta, rTMS is publicly funded and delivered, whereas in Quebec, rTMS is publicly funded and community delivered (i.e., fee-for-service); information on the funding model in Saskatchewan was not reported. Although it is not publicly funded in Ontario, patients were reported to receive rTMS treatment free of charge, with the cost covered by philanthropic, hospital, or research funds, depending on whether it was delivered in a research or clinical context.

Across Canada, rTMS was reported to be delivered in outpatient clinics, research studies, and private clinics and to be primarily delivered by technicians or nurses, under the supervision of physicians (psychiatrists). Training was reported to be provided by the Canadian rTMS distributor, a course developed at CAMH, and internally by rTMS-trained staff. Additional supports (e.g., help finding low-cost accommodation) were generally not reported to be provided to patients undergoing rTMS in a clinical context; some support (e.g., help with transit tickets, parking) was reported to be provided to patients in some rTMS research studies.

7 Systematic Review of rTMS Implementation Models

***Summary**:*

- Six studies were identified on implementation of rTMS for depression.
- Four themes related to implementation emerged across studies: assessment and safety, treatment room, personnel and training, and patient experience.
- Patient experience emerged as an essential factor for rTMS implementation across studies; patient comfort and psychoeducation are important factors for treatment tolerability and success.
- rTMS treatment should only be administered by trained staff.
- Parameters for rTMS treatment should be determined by a physician (e.g., a psychiatrist), and treatment may be administered by nurses or technicians under supervision.
- Assessment (e.g., contraindications, mood) should be conducted prior to starting treatment and continue throughout; changes in medication may require reassessment.

7.1 Purpose

To synthesize the available literature on implementation of rTMS for the treatment of depression.

7.2 Methods

7.2.1 Search Strategy

A systematic review was completed. The literature search was conducted by following the Joanna Briggs methodology.[49] MEDLINE, Cochrane CENTRAL, EMBASE, PsychINFO, the Cochrane Database of Systematic Reviews, and the Health Technology Assessment Database were searched for studies published from inception until March 18, 2020, with the exception of the Health Technology Assessment Database which was run up to the database's last update, March 31, 2018. Terms aimed at capturing the technology of interest, including "tms," "rtms," and "repeat tms" were combined with implementation terms, such as "administration," "implementation," and "staffing," using the Boolean Operator "and." Terms were searched as text words in titles and abstracts and as MeSH subject headings when applicable. The search was limited to English or French language studies, and a filter was used to exclude commentaries, editorials, and conference proceedings. The search strategy was developed by a research librarian. The full search strategy is available in Appendix B. The reference lists of included studies were hand-searched to ensure all relevant literature was captured. A search of the grey literature was not conducted.

7.2.2 Study Selection

Abstracts were screened in duplicate by two independent reviewers. Abstracts proceeded to full-text review if they: examined rTMS as treatment for a depressive disorder in humans (e.g., major depressive disorder), reported on one or more aspects of rTMS implementation such as staffing models, training programs, funding models, program evaluation, and program models, and were published in English or French. Citations were excluded if they failed to meet the inclusion criteria above, or if they: were not a study design of interest (e.g., editorials, letters to the editor), evaluated only the clinical effectiveness of rTMS therapy, reported solely on implementation of rTMS for a condition other than depression, or reported data from non-human or animal studies (Table 6). Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review. Full-text review was completed in duplicate by two independent reviewers. Any discrepancies between reviewers were resolved through discussion and consensus. If required, a third reviewer was consulted.

Table 6. Inclusion and Exclusion Criteria for Systematic Review of Implementation Models

Inclusion Criteria	Exclusion Criteria
• Focus on rTMS as treatment for depressive disorder • Reports on one or more aspects of rTMS implementation ○ Including, but not limited to: staffing models, training programs, funding models, program evaluation, and program models • Published in English or French	• Study design: editorials or letters to the editor • Only evaluated clinical effectiveness of rTMS • Reported on implementation of rTMS for any condition other than depression • Reported data from non-human or animal studies

Abbreviations: rTMS: repetitive transcranial magnetic stimulation

7.2.3 Data Extraction and Analysis

Data were analyzed using the 'best-fit' framework synthesis methodology.[50,51] This methodology is based on the framework analysis methodology, which has been widely used to synthesize

qualitative data for policy decision-makers.[52] 'Best-fit' framework synthesis involves the creation of an *a priori* thematic framework, which is used to subsequently guide coding and analysis. The process broadly involves seven phases: 1) defining a review question; 2) performing a systematic review of the literature; 3) developing an *a priori* framework using thematic analysis; 4) coding the included literature using this framework; 5) creating additional themes during the coding process that were not captured in the *a priori* framework; 6) developing a new framework using the *a priori* structure and new themes; and 7) examining the evidence to understand how the themes are related.[50,53]

After reviewing the included studies, a thematic framework was developed, as outlined by Carroll et al.[50] Using this framework, nodes and sub-nodes were developed in QSR's International NVivo 12 qualitative data analysis software.[54] This framework provided structure to coding and analysis and evolved throughout the coding process. Data were coded in NVivo by a single reviewer and verified by another. Discrepancies between reviewers during this process were resolved through consensus. A final framework consisting of both new and *a priori* themes was developed, and the resulting themes were synthesized narratively.

7.2.4 Quality Assessment

Quality assessment was not conducted because the range of study designs included in this systematic review precluded meaningful comparative quality assessment.

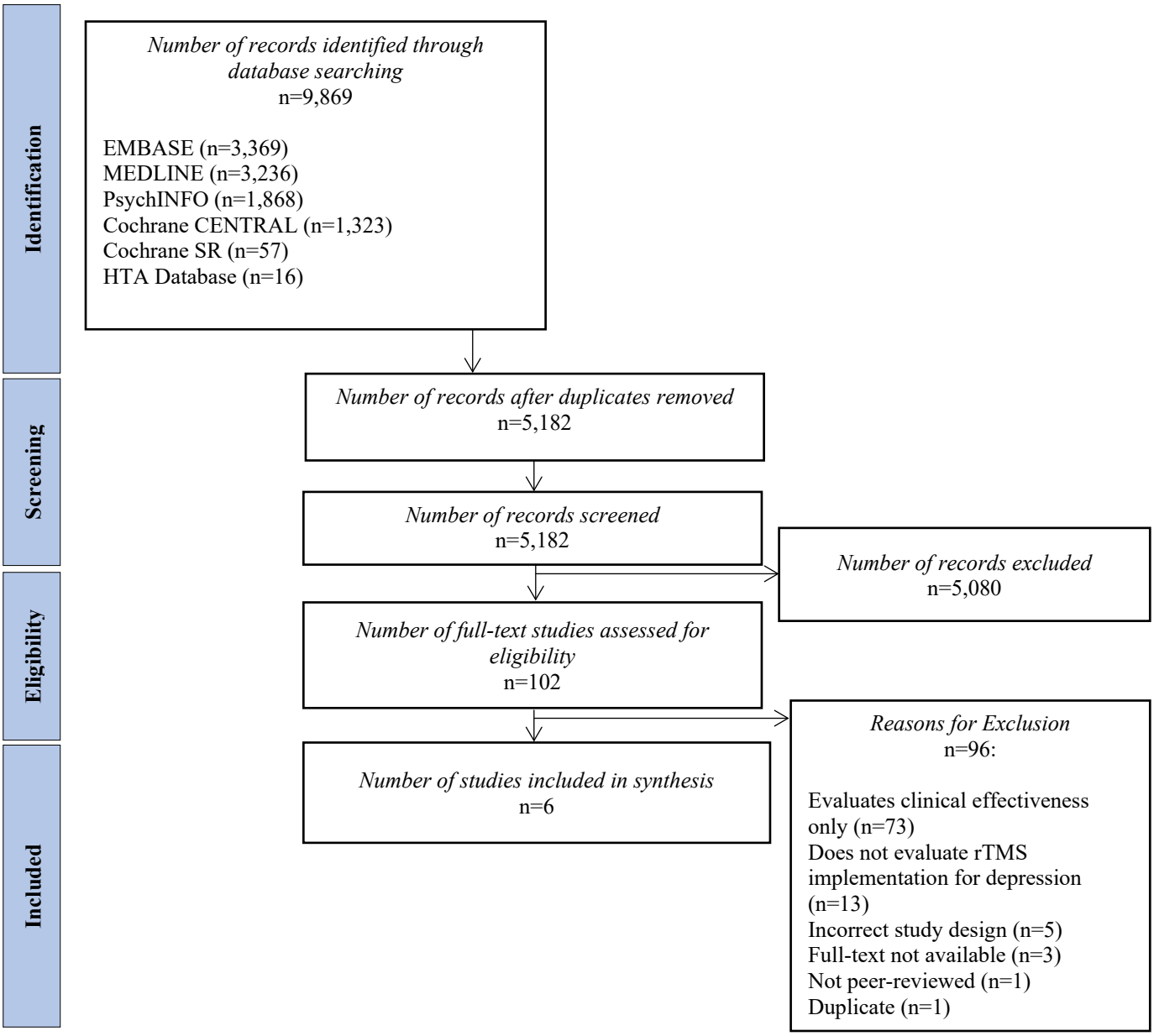
7.3 Findings

7.3.1 Study Characteristics

A total of 9,869 citations were identified from the literature search, as follows: EMBASE (n=3,369), MEDLINE (n=3,236), PsychINFO (n=1,868), Cochrane CENTRAL Register (n=1,323), the Cochrane Database of Systematic Reviews (n=57), and HTA Database (n=16). After duplicates were removed, 5,182 unique abstracts were reviewed. Of these, 5,080 were excluded, and 102 studies were assessed for eligibility in full-text. Ninety-six publications were excluded at full-text review for the following reasons: only evaluated clinical effectiveness (n=73); did not evaluate rTMS for depression (n=13); incorrect study design (n=5); not published

in full-text (n=3); not peer-reviewed (n=1); and duplicate (n=1). Six studies were included in the final narrative synthesis (Figure 6).

Figure 6. PRISMA Flow Chart of Included and Excluded Studies



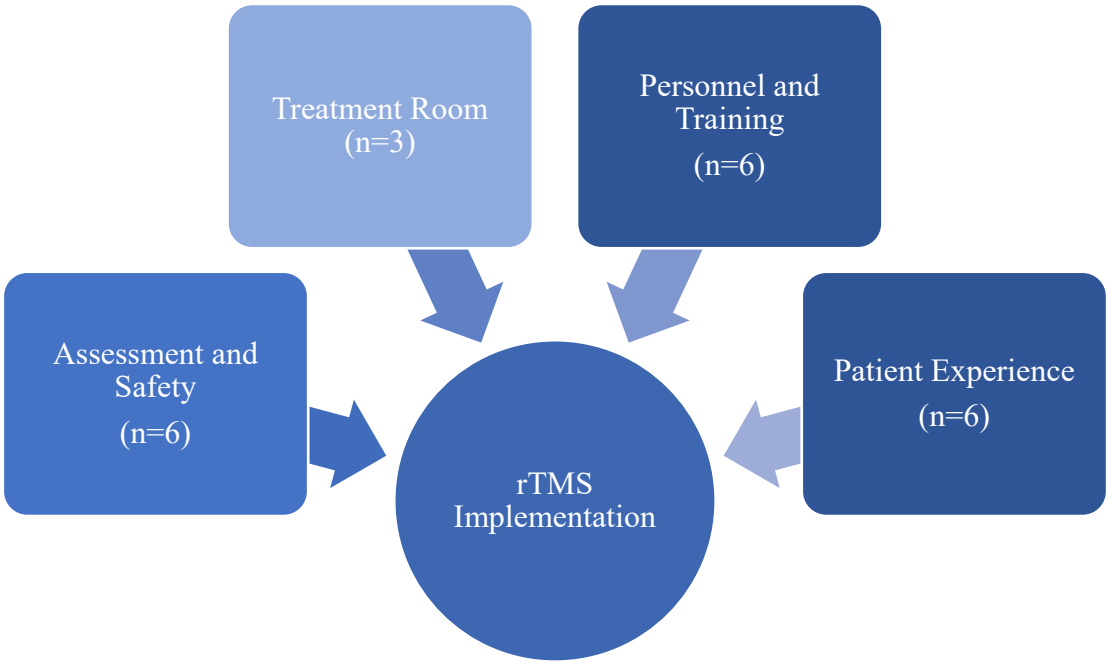
The included studies were published between 2009[55] and 2018.[56] Three studies were from Australia,[56-58] and three were from the United States.[55,59,60] Three of the included studies reported

on the experience of running an rTMS clinic, written by health care providers working in an rTMS clinic.[55,58,60] Two studies reviewed literature on techniques for prescribing and administering rTMS and provided recommendations based on this literature,[57,59] one of which included treatment recommendations from the Clinical TMS Society.[59] Lastly, one study reported an overview of the safety literature on rTMS for depression and provided recommendations for clinical practice.[56]

7.3.2 rTMS Implementation Themes

Four themes related to rTMS implementation emerged across included studies: assessment and safety, treatment room, personnel and training, and patient experience (Figure 7). A discussion of each theme follows below.

Figure 7. rTMS Implementation Themes across Included Studies



7.3.2.1 Assessment and Safety

Included studies described the importance of pre-treatment medical and psychiatric assessment, as well as continued monitoring of treatment safety and progress.[55-60] All studies recommended that patients be screened for contraindications to treatment (e.g., history of seizures, implanted metallic or magnetic devices).[55-60] One study noted that a risk/benefit analysis should be

conducted prior to undertaking treatment with the following patients: pregnant women, adolescents, patients with pre-existing neurological conditions, and patients with implanted electronic devices.[56]

Included studies stated that clinics offering rTMS must have emergency response protocols in place, access to emergency medical services at all times,[55,57,59] and be well-equipped to provide first-response to seizures.[56,57,60] It was noted that formal standard operating procedures relating to training and ongoing maintenance of procedural skills, as well as documentation of specific credentialing should be readily available and updated.[58-60] Lastly, studies recommended that rTMS operators adhere to standard rTMS safety guidelines.[56,58-60]

7.3.2.2 Treatment Room

7.3.2.2.1 Room Design

The rTMS suites described across studies included a treatment room, a waiting room, a nearby bathroom, an office, and a room containing an air conditioning unit for the rTMS coils.[57,58] Due to the loud sound of the rTMS machine, it was recommended to adequately soundproof the room or to locate it away from areas where loud sounds may be problematic.[57,58] Studies noted that guidelines on dealing with seizures should be posted in the treatment room,[55,60] and a panic button may be installed in case of emergency.[55] Cardiac defibrillators, intravenous access, suction, and oxygen were not felt to be necessary for the safe outpatient administration of rTMS.[59]

Described room features to enhance patient comfort during treatment included an extra chair in the room for a support person, earplugs, pillows, a TV with a DVD/VCR, a desk, a water fountain, and plants.[55] It was suggested that a pleasant scent, proper lighting, comfortable room temperature, muted wall and floor colours, and pictures of nature or landscapes may enhance patient comfort.[55]

7.3.2.2.2 rTMS System

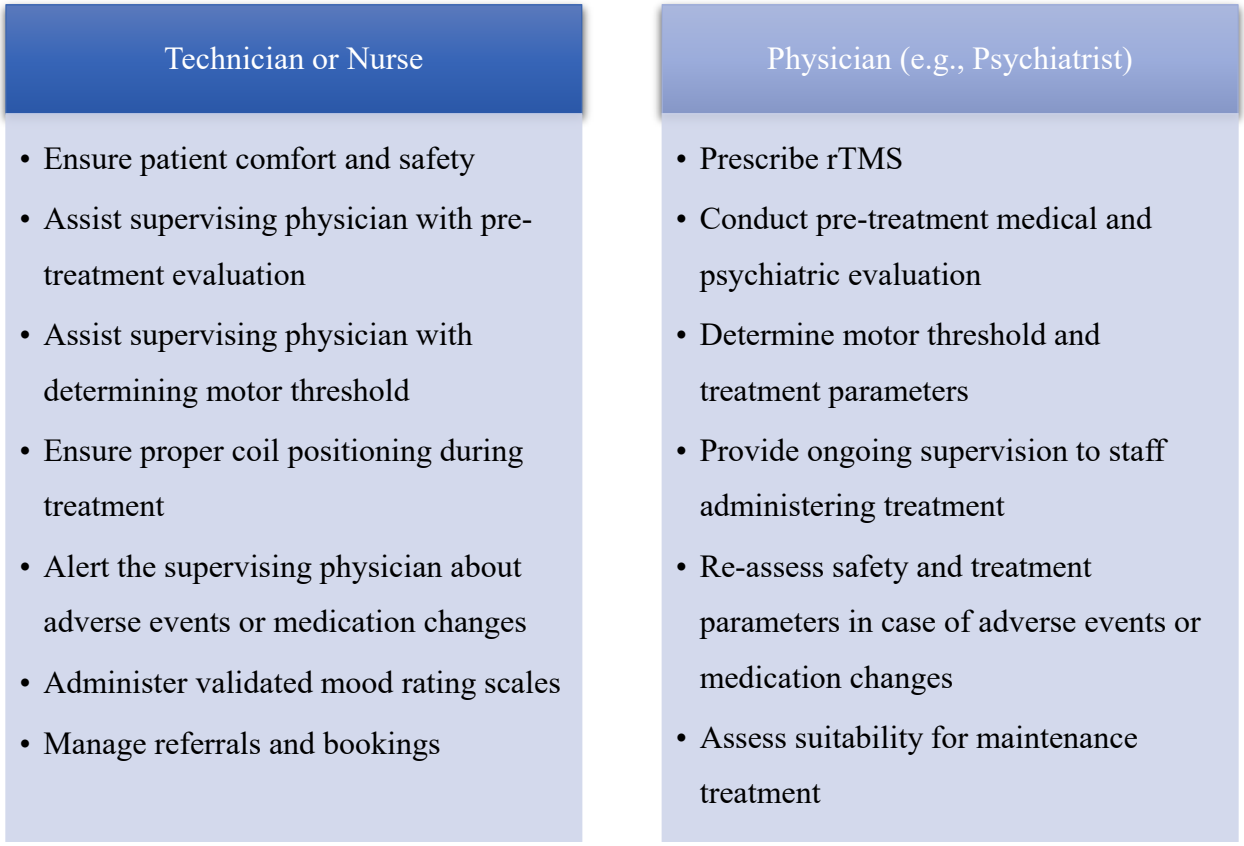
Studies did not consistently mention implementation considerations related to one particular rTMS device. One study noted that the following factors were important to consider when choosing an rTMS system:[57]

- capacity of the stimulator to stimulate at sufficient power and frequency,
- availability of coils that do not overheat during typical treatment sessions (and will cool sufficiently between scheduled treatment sessions),
- availability of accessories such as coil stands and devices to ensure the repeatability of coil positioning,
- ease of the coil manipulation during the measurement of motor threshold,
- flexibility of the stimulation protocols provided,
- ease of use of the software interface,
- potential requirement for multiple power sources,
- availability of a local repair service, training, and support,
- availability of a contingency plan in the event the equipment breaks down or needs servicing.

7.3.2.3 Personnel and Training

Across studies, rTMS was reported to be primarily administered by trained nursing staff or technicians under the supervision of an rTMS-trained physician (e.g., psychiatrist).[55-60] Responsibilities of the nursing or medical staff during treatment included ensuring proper coil positioning, ensuring patient comfort and safety, and alerting the supervising physician about adverse events or changes in medication.[60] Other responsibilities included assisting the supervising physician with initial patient evaluation,[55,60] managing referrals and bookings,[58] and administering validated mood rating scales to assess treatment progress.[60] Primary responsibilities of the rTMS-trained physicians included conducting the pre-treatment evaluation,[60] prescribing the rTMS treatment,[57] determining the motor threshold and treatment parameters,[60] re-assessing the patient in the event of changes to medication or medical status,[60] assessing suitability for maintenance treatment,[58] and providing ongoing supervision to staff delivering treatment sessions.[59]

Figure 8. Roles and Responsibilities in rTMS Provision



Included studies reported that rTMS should only be prescribed by an rTMS-trained physician (e.g., a psychiatrist) and administered by rTMS-trained staff.[55,57-60] Aside from receiving technical training from the rTMS manufacturer,[55,59] studies recommended for rTMS providers to have "first responder" training.[57,59] One study recommended that, depending on their expertise with rTMS, providers may need to undergo additional training either through peer-to-peer direct supervision or an industry-independent Continuous Medical Education program.[59] An example of peer-to-peer training was discussed in one study which reported a one-day training session provided by an rTMS expert to the clinic's service directors, nursing staff, and psychiatrists.[57] This training included assessment procedures, practical training in establishing the motor threshold and mapping the position of the DLPFC, operation of the rTMS device, and protocols and policies for treatment and research.[57]

7.3.2.4 Patient Experience

Psychoeducation and comfort emerged as major factors affecting patient experience with rTMS across studies. Importantly, the included studies represent the perception of patient experience from the rTMS providers, rather than the patients, and should therefore be interpreted as such.

7.3.2.4.1 Psychoeducation

Studies reported that rTMS psychoeducation should begin with the patient's initial contact with the clinic and should continue to be provided throughout the treatment process, as required.[55,60] One study noted that they begin this process by sending interested patients a "welcome packet" which includes information about rTMS and the program at their clinic.[55] When patients arrive at the clinic for their first visit, they are encouraged to sit in the treatment chair and watch an educational video explaining the rTMS procedure.[55] Because the first orientation and evaluation visit may be stressful for the patient, the nursing staff try to make the patient comfortable by providing empathy and support and by encouraging them to ask questions.[55]

Several studies noted that pre-treatment psychoeducation should involve a thorough discussion of the risks and benefits of the treatment, including the risk of seizures,[57] manic switching,[56] vasovagal syncope which can occur during initial sessions,[59] and the importance of informing the treatment team about changes in their medication status or medical condition.[57] Patients should be offered reassurance that protection against these risks will be offered.[55] Appropriate expectations should also be set regarding treatment course and benefit.[59]

7.3.2.4.2 Comfort

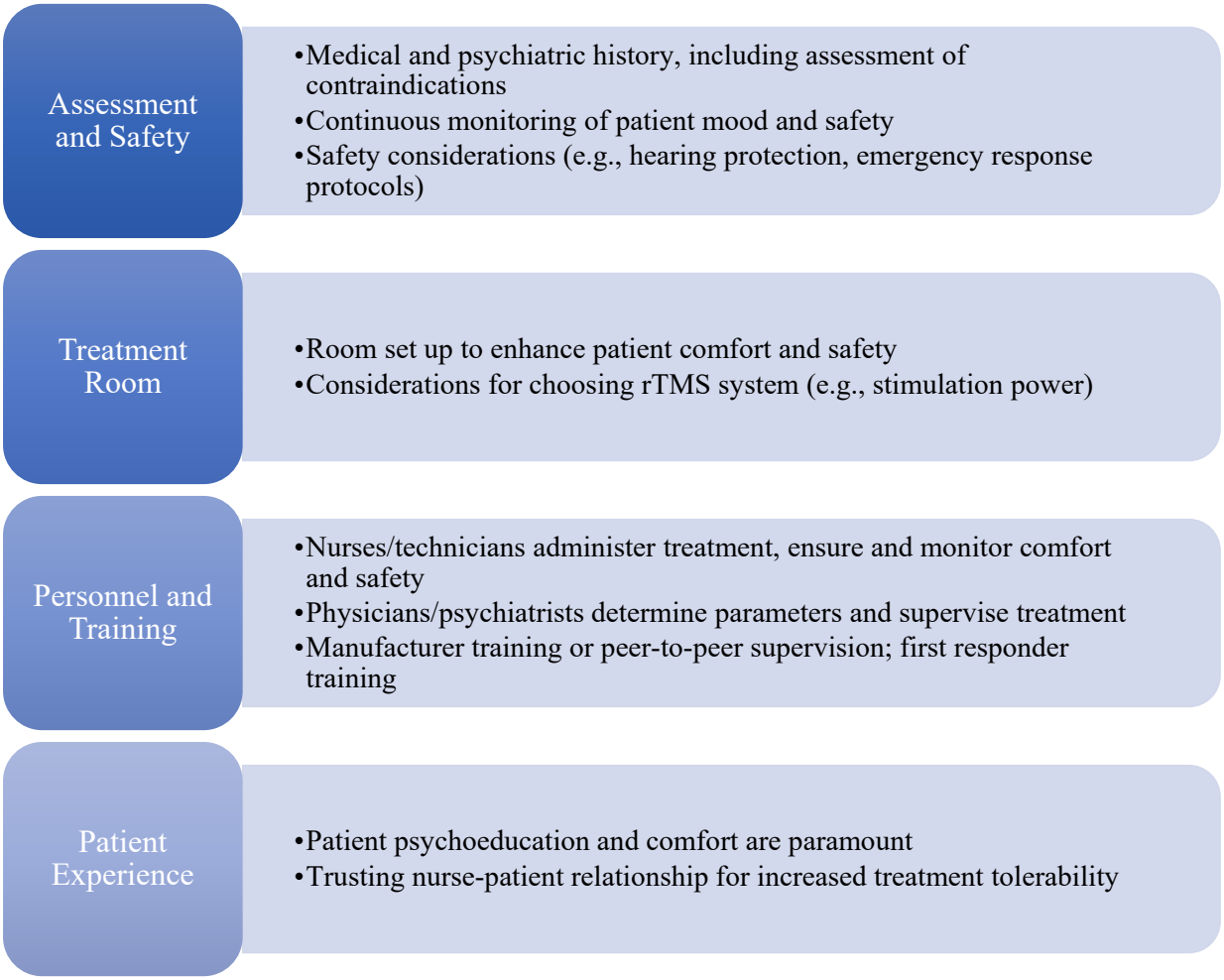
Included studies reported that nursing staff play an essential role in ensuring patient comfort and safety during rTMS treatment.[55,60] This included patient positioning during treatment, such as ensuring that the patient has a comfortable recliner chair,[58] and providing the patient with small cushions for proper head, neck, and lumbar support to increase treatment tolerability.[60] Several studies noted that nursing staff should be empathic, knowledgeable and should promote an atmosphere where the patient feels comfortable asking questions or reporting adverse effects.[55,60] Patients should be informed of the discomfort they may feel during treatment, and providers may

engage them in conversation to increase treatment tolerability;[55] it was recommended that treatment tolerability and patient well-being be assessed after each session.[56]

7.4 Conclusion

Based on the results of this systematic review, several factors need to be considered when implementing an rTMS service for treatment of depression: assessment and safety, treatment room, personnel and training, and patient experience (Figure 9).

Figure 9. Synthesis of Implementation Considerations



Patient psychoeducation and comfort emerged as recurring themes throughout studies and should be considered when designing the rTMS treatment room and administering treatment. Given their involvement in all stages of the treatment process, nursing staff have a significant impact on

the patient experience of rTMS; therefore, the creation of a trusting nurse-patient relationship is paramount to treatment success. Treatment room comfort can be enhanced by adding a comfortable chair and pillows, muted wall colours, artwork featuring nature, and relaxing music. Safety precautions should include hearing protection for the patients and operator, first responder training, and emergency response protocols.

Similar to nursing staff, rTMS-trained physicians should be involved in all stages of the treatment process; however, their involvement should centre on conducting the pre-treatment assessment, determining the motor threshold and treatment parameters, and supervising the staff that deliver the treatments. Pre-treatment assessment should include an evaluation of the patient's medical and psychiatric history, including any contraindications to treatment, and these factors should be continuously monitored throughout treatment to ensure success and tolerability. Lastly, rTMS should only be prescribed by physicians (e.g., psychiatrists) and administered by trained staff; rTMS training should be obtained from the device manufacturer and/or peer-to-peer supervision; all providers should have first responder training and be versed in the emergency protocols in the event of adverse treatment effects.

8 Clinician Interviews

Summary

- From the interviewees' perspective, BC has a treatment gap for patients with TRD who have not responded to or are intolerant of antidepressants, and ECT is not an option. rTMS was perceived to be well-positioned to bridge the treatment gap for these patients, given the established body of effectiveness literature and relative ease of administration.
- Health care providers perceived patients with TRD to be very interested in rTMS as a treatment option.
- Access to rTMS in BC was reported to be inequitable, as it is currently only offered in a few clinics in Victoria and the Vancouver region. Current access was perceived to be further limited by the high cost of the treatment, the need to pay for accommodations out-of-pocket, and the time commitment associated with daily treatment administration for working individuals.
- Proposed models for implementation of rTMS in BC included community clinics and in-hospital administration.

8.1 Purpose

To understand key considerations for implementing rTMS for TRD in BC by exploring clinicians' perceptions of rTMS, including the current care pathway, opinion on effectiveness and need for alternative treatments, patient acceptability, barriers to access, and future care models.

8.2 Methods

8.2.1 Data Collection

Qualitative interviews were conducted by telephone with a purposive sample of clinicians. A snowball sampling approach was taken; clinicians initially identified by the BC Ministry of Health, and who agreed to be interviewed, were asked to identify other potential clinicians to contact. An effort was made to speak with clinicians from each health authority.

A semi-structured interview guide was developed; it was piloted with two clinicians and subsequently refined. This guide included questions on clinician perceptions of rTMS for TRD, including the current care pathway, opinion on effectiveness and need for alternative treatments,

patient acceptability, barriers to access, and future care models. The full interview guide can be found in Appendix C.

8.2.1 Analysis

All interviews were conducted by an experienced, PhD-trained qualitative researcher, audio-recorded with the consent of the interview participants, and detailed notes were taken. The interviews were then transcribed for analysis.

The data were analyzed using the framework analysis methodology,[61,62] a form of qualitative content analysis, which is used to draw descriptive conclusions based on themes. Originally developed for policy research, this qualitative methodology is particularly useful for synthesizing data in order to support policy questions. Framework analysis involves categorizing data according to key issues and themes[62] and broadly involves seven stages: 1) transcription of the interviews; 2) familiarization with the interviews; 3) coding the interviews; 4) developing a working analytical framework; 5) applying the analytical framework to the existing categories and codes; 6) charting the data into the framework matrix; and 7) interpreting the data.[61]

After the interview transcription and familiarization processes were completed, the interviews were coded in QSR's International NVivo 12 qualitative data analysis software.[54] Data were coded by a single reviewer and verified by a second reviewer. Discrepancies between reviewers during this process were resolved through consensus. A working analytical framework that fit the interview data was developed and subsequently applied to the existing categories and charted in NVivo. Peer-debriefing was performed throughout all phases of the analysis process, following best-practice criteria set forth by Nowel et al. 2017.[63]

8.3 Findings

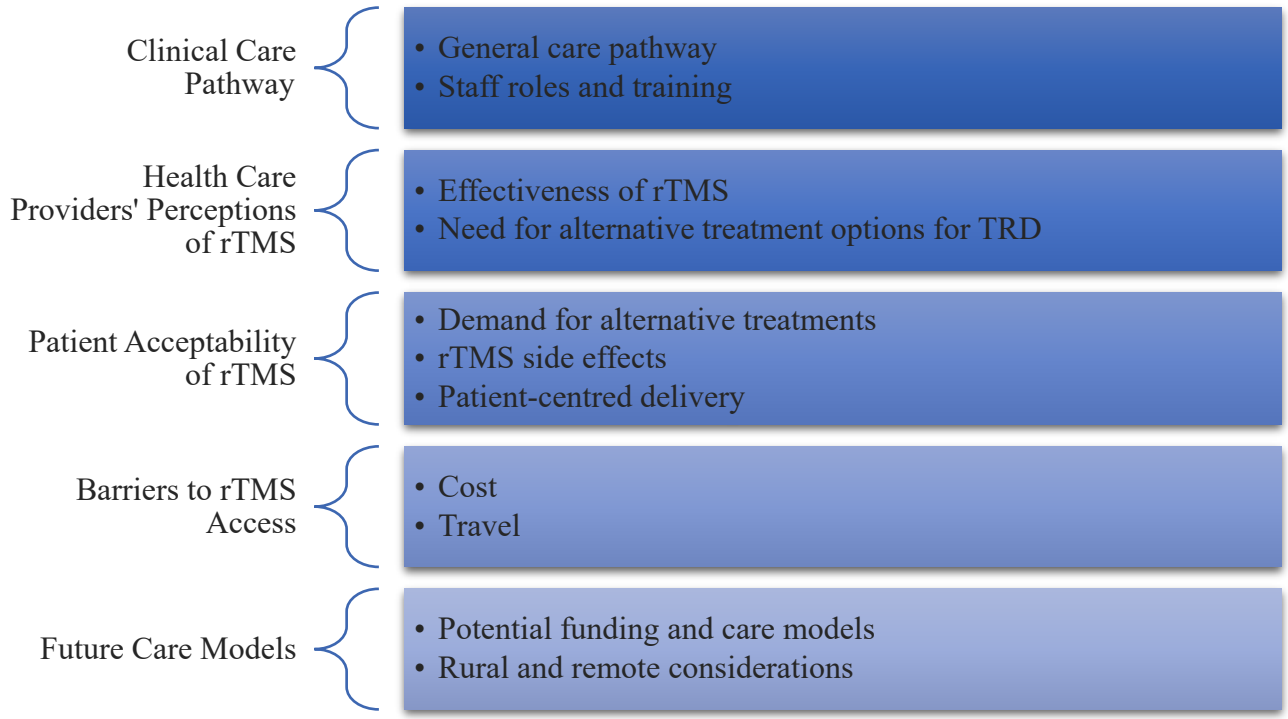
8.3.1 Participants

Telephone interviews were conducted from March – May 2020 with seven health care providers: six psychiatrists and one rTMS technician. The interviews ranged in length from 56 to 87 minutes. Four health care providers were from Vancouver Coastal, one from Vancouver Island Health, one from Northern Health, and one from Interior Health. Of the seven health care

providers interviewed, four reported currently administering rTMS, one reported administering it in the past, and two have training on rTMS but have not yet administered it.

The following five themes were identified in this analysis: current care pathway, health care providers' perceptions of rTMS, patient acceptability, barriers to access, and future care models (Figure 10).

Figure 10. Themes and Subthemes in BC Health Care Provider Interviews



8.3.2 Clinical Care Pathway

8.3.2.1 General Care Pathway

Health care providers reported that most BC patients with TRD are treated by general practitioners (GPs) (Figure 11). When treating TRD patients in their own practice, health care providers noted that they cycle through different antidepressant medications prior to progressing to other treatment options, such as antipsychotic medications, rTMS, or ECT. Health care providers mentioned the CANMAT guidelines for neurostimulation for depression, noting that the guidelines recommend rTMS as first-line treatment after failing at least one trial of

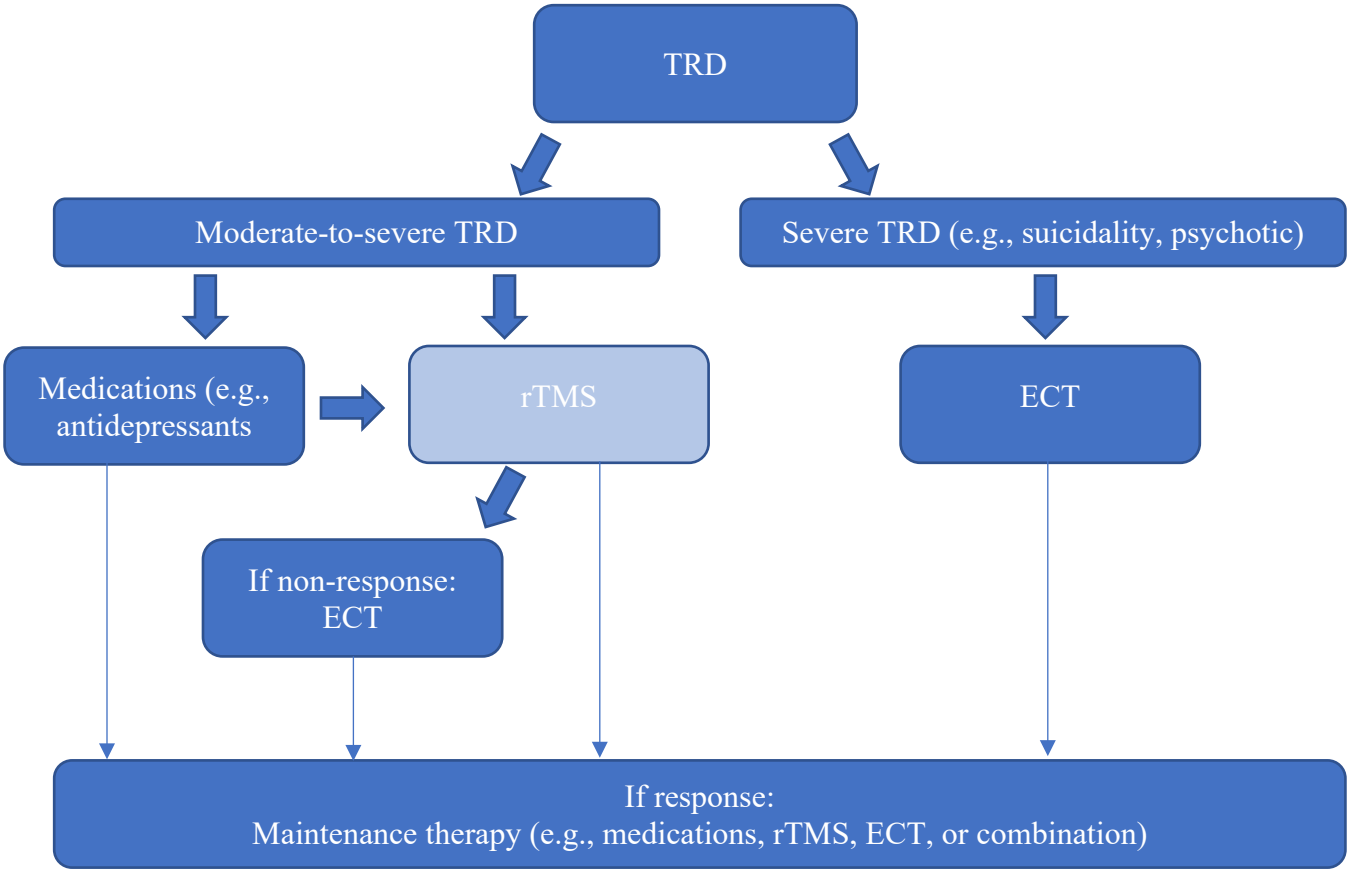
antidepressants. To access rTMS treatment in BC, patients require a referral from their GP or a psychiatrist; however, it was noted that patients can also access rTMS as part of a clinical trial at the University of British Columbia without a referral. In BC, rTMS was reported to be offered in one research and clinical centre in Vancouver, a non-profit clinic in Vancouver, two private clinics in the Vancouver region, and one private clinic in Victoria.

rTMS was described as appropriate for patients who have tried several antidepressants without success or patients who are unable to tolerate antidepressants due to side effects:

> *"...if a patient comes in and they've tried numerous antidepressants. It hasn't worked for them, or if they've tried one, or tried psychotherapy and things have not gotten better. Then we will offer them rTMS. But then there's another group of patients who have... they're just not able. They're not really treatment resistant because they do show some efficacy on the medications. They're just not able to tolerate the medications because of side effects. If the side effect burden of the medication is too much, then we offer (r)TMS."*

Several health care providers perceived rTMS as the preferred treatment option for these patients prior to trying ECT, due to rTMS being less invasive and having fewer side effects. rTMS contraindications discussed by the providers included a history of epilepsy or implanted metal hardware, such as a pacemaker, but it was noted that most patients they see do not have these contraindications. ECT was perceived to be a treatment that is more appropriately administered after rTMS or for patients with severe depression, who have failed several treatments, are psychotic, or suicidal: "*If the severity is significant, or they feel that they've exhausted medication trials, the next option is ECT*." rTMS was judged to be an insufficient treatment for these populations due the perceived greater efficacy of ECT; ECT was often described as the standard of care but limited by its invasiveness, greater side effects, and the personnel and resource requirements involved with anaesthesia and clinical administration.

Figure 11. General Care Pathway for Patients with TRD in BC



Abbreviations: ECT: electroconvulsive therapy; rTMS: repetitive transcranial magnetic stimulation; TRD: treatment resistant depression

8.3.2.2 Staff Roles and Training

In exploring how rTMS could be implemented in BC, health care provider interviews were probed around the human resources required to properly administer the treatment. Two key roles involved in rTMS administration emerged across interviews: the role of psychiatrists and the role of technicians (Table 7). Across interviews, the role of psychiatrists was of a supervisory nature, including conducting assessments and prescribing treatment; configuring machine settings; training and supervising technicians delivering rTMS; monitoring patients throughout treatment and maintenance; and discussing concerns with patients related to treatment, side effects, and suicidality. It was noted that psychiatrists become qualified to administer rTMS through supplementary training. The four psychiatrists administering rTMS reported learning generally about rTMS as part of their psychiatric residency, but most reported seeking out additional

training to administer the treatment. This included a PULSES course by the TMS Society in the United States, a Harvard rTMS course, and a course delivered at American Psychiatric Association (APA) meetings. It was noted that few trainings for rTMS currently exist in Canada.

Technicians were reported to be the primarily administrators of the rTMS treatment. Their responsibilities included delivering the treatment using parameters and machine settings specified by the supervising psychiatrist; documenting side effects; and supervising junior rTMS technicians. No designated credentials for rTMS technicians were reported; however, most health care providers indicated a preference for technicians with some post-secondary training in psychology, science, or health care. Across interviews, technicians were drawn from graduate-level counselling students, as well as individuals with bachelor's degrees and nursing degrees. rTMS-specific training for technicians largely consisted of in-house training provided by psychiatrists or trained technicians, which consisted of shadowing the trained individual and learning proper coil placement. The reported length of technician training ranged from 10 hours to two weeks. Despite a lack of a formal credentialing process for rTMS technicians, interviewed health care providers stressed the importance of high-quality training in informing proper treatment administration.

Table 7. rTMS Staff Roles and Training

Role	Responsibility	General Training	rTMS Training
Psychiatrist	• Assess and prescribe treatment • Determine treatment parameters, including machine settings • Train and supervise technicians • Monitor patients throughout treatment and maintenance • Discuss concerns with patients (e.g., treatment, side effects, suicidality)	• MD + psychiatric residency	• Psychiatry residency • PULSES course by TMS Society in the US • Harvard rTMS course • Course at APA meetings
Technician	• Deliver treatments using pre-determined treatment parameters and machine settings • Document side effects • Supervise more junior technicians	• Bachelor's degree • Nursing degree • Graduate students in-training (e.g., counselling program)	• In-house training (e.g., shadowing an rTMS-trained technician or psychiatrist, learning the coil placement), ranging from 10 hours to two weeks • CPR course

Abbreviations: APA: American Psychiatric Association; CPR: cardiopulmonary resuscitation; MD: medical doctor; rTMS: repetitive transcranial magnetic stimulation; US: United States

8.3.3 Health Care Providers' Perceptions of rTMS

8.3.3.1 Effectiveness of rTMS

Health care providers expressed great enthusiasm about rTMS, perceiving it to be a well-known treatment with established efficacy for treating TRD:

> *"It's not new, this treatment. It has a lot of evidence. The research for it is difficult to do, but despite that, I think there are more than 15 meta-analyses that are positive. And really even the new studies show that it's a technology that will evolve. And I don't think even with what we have, I think it's enough for us to... I think it's just fair for us to be able to offer our patients, this new treatment. And the science shows that it could replace much more invasive treatments like ECT."*

It was noted that the body of evidence on rTMS is evolving, with emerging research on different rTMS protocols (e.g., shorter duration) and its use for other indications (e.g., obsessive-compulsive disorder). Overall, there was a sense that the efficacy of rTMS for TRD has been established, and that the field has moved on to examining its effectiveness in real-world populations, optimizing the current treatment protocols, and looking at whether it may be used for other indications. As a result, some health care providers felt that implementing rTMS in BC could be cost-effective over the longer term as the treatment may become useful for a broader range of disorders.

In practice, health care providers currently administering rTMS for TRD observed a response rate that ranged from 50-75%; one provider noted that they observe higher response rates in their clinic than what is reported in the clinical trials in the literature. Another health care provider described their patients' experience as falling into three categories: responders whose symptoms decrease by at least half, responders who do not improve as much, and non-responders.

Broadly, health care providers who have administered rTMS perceived it to be a positive experience for their patients, many of whom have been suffering from TRD for many years. They describe patients who, because of rTMS, can return to work or take up increased childcare responsibilities. One provider described having a wall of "thank you" cards from their patients who have experienced relief, noting a particular card from a patient expressing gratitude that read: "*Thank you. I feel like I'm having a brand-new brain. It's been a while since I enjoyed Christmas*."

8.3.3.2 Need for Alternative Treatment Options for TRD

Interviewed health care providers strongly advocated for rTMS as an alternative treatment option for patients with TRD who either have tried and not responded to antidepressants, cannot tolerate antidepressants, are not ill enough to require ECT, or do have access to ECT. There was a sense across interviews that these patients are "falling through the cracks" of the current system:

> *"…this big group of patients just has no accessible treatment because they're not quite sick enough to access ECT from our hospitals, but they're not*

responding to medications. This big group of patients is just falling through the cracks. TMS is not the only treatment for that group of patients, but it is one of them, and it should be... it's too bad that they can't access it as easily"

Health care providers stressed the debilitating nature of depression, describing it as a disorder that has ripple effects on people around the patient, including their families and their children, noting that the societal costs of depression are difficult to estimate.

8.3.4 Patient Acceptability of rTMS

8.3.4.1 Demand for Alternative Treatment Options for TRD

Health care providers perceived that patients with TRD were interested in alternative treatment options to antidepressants, particularly those that have experienced adverse side effects as a result of pharmacological treatment. As one provider noted: *"I think there's perhaps an intrinsic bias in who comes seeking for TMS, in that our people who probably have experienced significant side effects from medications or have tried medications and they've never helped, and so they really want something that is non-medication."* One health care provider described observing a sense of desperation among patients seeking rTMS:

"Well, some of them are already... by the time they come to my place, they've already looked into it themselves and it's something they want already. They want it. They wish that it was covered by government funding. They express frustration that's it's not. Out of desperation, they're seeking treatment despite the cost."

Patient demand for rTMS in BC was further stressed by one previous rTMS provider who explained that they continue to receive patient referrals three years after losing funding for their rTMS clinic. Another health care provider who currently administers the treatment described having almost 1,000 patients in their clinic chart. Overall, there was a sense across health care provider interviews that patients in BC are interested in receiving rTMS.

ECT was described as an alternative treatment option for more severe depression with psychosis or suicidality and as a last-line option for patients with moderate TRD who have not responded to rTMS. However, health care providers highlighted the extent to which receiving ECT is stigmatizing for patients, which in turn creates a barrier to access: "*People do face a lot of stigma and a sense of shame [with ECT] that it's something that they cannot share with anyone. It's a barrier that is significant*." An additional barrier is that ECT cannot be accessed on an outpatient basis without post-treatment supervision, due to the anesthesia required during administration.

8.3.4.2 rTMS Side Effects

Health care providers administering rTMS reported that their patients appreciate that side effects of rTMS are limited to within two hours of treatment, compared to the longer-term side effects of antidepressants or ECT. Notably, ECT was reported to be associated with long-term cognitive effects: "*[ECT] side effects are a major concern, particularly the memory. Even though they tend to be transient and go away within three to six months, but there is an impact, for sure*."
In comparison, the most common side effects of rTMS were reported to be involuntary jaw movement and site pain during treatment. Health care providers noted that seizures are a rare side effect of rTMS but none of the health care providers interviewed had observed an rTMS-induced seizure in their practice. Overall, health care providers administering rTMS did not view the treatment's side effects to be a barrier to treatment: "*I've never encountered any patient that dropped out because of side effects. That's also reflected in our clinical trials as well."*

8.3.4.3 Patient-Centred Delivery

Interviewed health care providers emphasized the importance of delivering rTMS in a patient-centred manner. Examples highlighted from their own practice included having the patients see the same technician for all their treatments at the same appointment time and having a place for a support person to sit in the treatment room with them. One provider felt that seeing the same technician every day was a positive experience for their patients:

> *"The aspect of interacting with the same technician day in and out, it's a constant positive comment. It's like, "Oh, I come here, and I see X, Y, or Z and they are terrific." Some people go as far as to say, "Oh, this is the highlight of my day.*

> *Before this, I was at home, would not see anyone, would not leave my bed. Now I have a purpose. I just go to the clinic and I see you guys every day. That is quite a constant."*

Current rTMS providers reported that although most patients come in for their treatment alone, extra seating is available in the treatment room for a support person to sit with them during the procedure. It was noted that patients become less reliant on their supports as the treatment progresses and they become more familiar with the process. By incorporating aspects of patient-centred delivery in their rTMS treatment process, health care providers felt that it resulted in a more positive experience for their patients.

8.3.5 Barriers to rTMS Access

8.3.5.1 Cost

With only one free rTMS treatment clinic in BC, health care providers frequently mentioned cost as a barrier for their patients: *"I would say probably, I don't know, half that don't... maybe half the people that don't do [rTMS], for half of them, it's the cost."* A course of rTMS at a private clinic was estimated to be around $3,000; it should be noted that this figure was reported by health care providers who did not work in private rTMS clinics. A not-for-profit clinic in Vancouver was reported to offer rTMS at a reduced, but still relatively high, cost (around $1,200 per treatment course).

Health care providers described how some patients are willing to pay the high treatment cost out of desperation, but generally expressed frustration at the prohibitive cost of rTMS treatment limiting access for vulnerable populations: "*So we're fortunate in that we're supposed to have universal health care and universal access, but the people who need this treatment the most are the ones who are going to have the most barriers to getting it*." Health care providers explained that many patients with TRD frequently face challenges with employment and meeting other basic needs: "*for these patients, even getting out of bed is a challenge*." As a result, having to pay a high treatment cost out-of-pocket may be perceived to be an insurmountable barrier for these patients who may benefit from the treatment the most.

8.3.5.2 Travel

Since rTMS is currently only offered in Victoria and the Vancouver, travel was reported to be a major logistical barrier to accessing rTMS in BC. Given that typical treatment protocols require administration five days per week for several weeks, patients who do not live within driving distance of a treatment centre must temporarily relocate, necessitating short-term accommodation and related costs of travelling and living away from home; this was reported to be a substantial barrier to patients living in Northern BC and the Interior where rTMS is currently unavailable. As a result of relocating, patients would also need to consider leaving behind their work, family, and community for an extended period of time. One health care provider from Interior Health reported that travel influenced their decision to not refer their patients for rTMS:

> *"So, I have not referred in few years. I remember discussing with patients about that option on few occasions, but really going to Vancouver is prohibiting and paying for it. Keep in mind that the majority of patients, when they get to that stage, face quite significant financial difficulties. And on top of that to say, "Well, you need to go and stay in Vancouver and pay for six weeks." That's not easy. Yeah, so I haven't had any patient actually going to Vancouver for treatment."*

Some health care providers reported that even for patients living within driving distance of the treatment centre, the daily treatment protocol can be demanding, particularly if they are working full-time and need to fit the treatment around their work schedule. Despite this, rTMS providers perceived that patients are eager to receive the treatment:

> *"When I started, I thought, "Oh, my God, this is going to be terrible. People are just going to stop coming. We are out in the woods...." I was quite concerned about it. To my surprise, we started to do the trials, we started to do them in clinic, and people would just come nonstop. The dropout rates in the trial are less than or around 5%."*

8.3.6 Future Care Models

8.3.6.1 Potential Funding and Care Models

To explore health care provider perceptions of rTMS implementation models, health care providers were asked about how they think rTMS might be best implemented in the BC context, along with benefits and drawbacks of each.

8.3.6.1.1 Community Clinics/Fee for Services

Several health care providers advocated for a community clinic/fee-for-service model. The clinic would be set up like a family practice clinic, with the psychiatrist responsible for hiring and training the rTMS technicians and maintaining a high quality of treatment. Proponents of this model felt that offering rTMS in a community setting would be more efficient than offering it in-hospital:

> *"...I would say if we were trying to be fair and give everybody access, then sometimes you're better off letting people use the community. Because if I'm really committed to TMS, I'm going to look around, I'm going to try to find the best facility, I'm going to be able to be the one who hires those technicians and trains them and stays involved with them, without levels of bureaucracy to swim through to try to get something working. And I can maintain a high quality, whereas I can't always maintain that quality in a hospital setting, which is really terrible to say but it's the absolute truth. There's just too many levels of bureaucracy. It just is kind of a little unfortunate."*

However, health care providers also worried that offering rTMS outside of a hospital may result in diminished quality control, particularly if treatment administration guidelines are not closely followed: "*There is the risk, if it's a for-profit type of clinic, to increase your margin. Sort of cost can be cut in certain ways, or procedures can be skipped or modified*." Since there is currently no specialty credential required to administer rTMS, there were also concerns that such an approach could quickly drain public funds. As a result, health care providers recommended that a fee-for-service model have specific requirements, such as ensuring that appropriate training has been obtained.

8.3.6.1.2 In-Hospital Provision

Health care providers advocating for in-hospital delivery of rTMS felt that there were several advantages to delivering rTMS in this environment. First, they noted that a hospital environment offers the best support for dealing with the potential side effects of rTMS, such as seizures. As one provider noted:

> *"Also, there could be side effects with TMS, especially if it's giving five times per week, which could be giving as well. And so, five times a week, 40 minutes, for four to six weeks, increases the risk of having those side effects the more numbers you have. So, seizures, somewhere that you are far away from hospital, one needs to deal with that. Yes, it's possible, but I don't think it could be as safe I'll say as in a hospital monitored by nurses, or with physicians on site."*

In addition, health care providers felt that offering rTMS in-hospital would maintain good quality control through more stringent requirements for both patients and those administering the treatment. However, providers reported that the costs of offering rTMS in-hospital would be higher than offering it in the community: "*It seems really high cost because there's a really high cost in running a program through a hospital, right? Because everything has to be very formalized. There's a lot of admin overhead.*"

8.3.6.1.3 Offer in ECT Clinics

Several health care providers suggested that rTMS be paired with a service already offering ECT, noting that the psychiatrists offering ECT have to go through a hospital privileging process, ensuring that they stay current on their training, which was felt to increase quality control. It was perceived that this administration model would be conducive to a cross-provincial distribution of the service and would ensure standards of practice:

> *"...Pairing the TMS to neurostimulation services makes a lot of sense and has a lot of advantages, in that you can create ECT services across the province. Geographically, you could have in Prince George, Kelowna, Kamloops, Vancouver Island, Victoria, Nanaimo, Fraser. You can distribute, I don't know,*

10, 15 centers across the province that geographically reach to 95% of the population in BC. In that way, if it's a network, the cost is going to be a lot less than a fee-for-service model. You're going to ensure standards of practice."

8.3.6.2 Rural and Remote Considerations

Health care providers also offered suggestions for implementation of rTMS in rural and remote areas of BC. Several providers discussed the possibility of a virtual care model that would consist of a qualified privileged psychiatrist located in an urban centre instructing the on-site rTMS clinician in a remote clinic on issues surrounding treatment and patient care. Providers discussed seeing their patients virtually as a result of COVID-19 and felt that this model may translate to rTMS administration for rural and remote regions of the province. Other suggestions included capitalizing on new treatment protocols that shorten the treatment time from six weeks to 14 days, which may make relocating to an urban centre more manageable, and helping patients find low-cost accommodations during their treatment course of rTMS.

Health care providers across rural and remote locations differed in their perceptions of whether they have the appropriate infrastructure to implement an rTMS service. Two providers working in hospital settings felt they were well positioned to deliver rTMS. However, one health care provider from Northern BC felt that bringing rTMS to the north of the province may require additional infrastructure, particularly if choosing to pair rTMS with an ECT service, noting that some areas are under-resourced. The current infrastructure to administer ECT was described as sub-optimal:

"…we have a very old hospital, we have a really old psychiatric ward that's dangerous and really non-therapeutic. So, we have a terrible place to deliver ECT, so there would have to be some infrastructure that would be looked at to even bring things to standard in the North because unfortunately, the North… some areas I think are well-resourced and others aren't, and it's a little bit of patchwork there."

8.4 Conclusions

Seven BC health care providers were interviewed about their perspectives on implementation considerations for rTMS in BC. Health care providers felt that BC has a treatment gap for patients with TRD who have not responded to or are intolerant of antidepressants, are not ill enough to require ECT, or cannot access it. rTMS was perceived to be well-positioned to bridge the treatment gap for these patients, given that it has an established body of literature, does not require extensive training, and is relatively easy to administer. Health care providers perceived rTMS to be cheaper than ECT, and all agreed that patients with TRD were very interested in rTMS as an alternative treatment option to medications and/or ECT.

Context for rTMS administration in BC was limited, given that rTMS is currently only offered in five clinics across BC (four clinics in the Vancouver region and one in Victoria). Access was reported to be inequitable and was perceived to be further limited by the high cost of the treatment, the need to pay for accommodations out-of-pocket, and the time commitment associated with daily treatment administration for working individuals. This means that certain subsets of the population, including those living outside of the greater Vancouver region, and those constrained by financial resources, are particularly disadvantaged when it comes to accessing rTMS. Health care providers discussed several models of implementation of rTMS into the BC health system, which included community clinics or in-hospital administration, stressing that both options are associated with corresponding benefits and drawbacks. They also noted that there is the potential that implementing rTMS in BC could have longer term benefits as more research continues to be undertaken exploring the broad application of rTMS for a variety of conditions.

9 Rapid Qualitative Review of Patient Perspectives

Summary

- A rapid review of the qualitative literature on patient and caregiver perspectives on rTMS was conducted by the Canadian Agency for Drugs and Technologies in Health.
- One study met the inclusion criteria and was included in the CADTH report, which explored reasons for self-referral for rTMS.
- The included study concluded that the reasons for self-referral were heterogenous, revealing that rTMS had broad appeal across age groups and for various reasons.

9.1 Purpose

To summarize the findings of a rapid review of the qualitative literature on patient perspectives on repetitive transcranial magnetic stimulation (rTMS) conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH). The full CADTH report can be found in Appendix D.

9.2 Overview of CADTH Methods

A rapid review of the qualitative literature on patient perspectives was conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) on behalf of the HTA Unit at the University of Calgary. The rapid review sought to describe the patient's and health care provider's experiences, expectations, and perceptions of rTMS.

9.2.1 Literature Selection

A literature search was conducted by an information specialist in OVID Medline/PsycINFO, Scopus, and CINAHL, and was limited to English language and studies published between January 1, 2014 and April 23, 2020. The main search concepts were rTMS and depression, with a search filter limiting retrieval to qualitative studies only. One reviewer screened citations and selected studies. For additional methodological details, see full report in Appendix D.

9.2.2 Summary of Evidence

One primary qualitative study met the inclusion criteria and was included in the CADTH report. It explored the reflections of people living with TRD regarding their expectations for and experiences with rTMS. No relevant primary mixed methods studies were identified. No studies

investigated health care providers' experiences with and the perceptions of rTMS as a potential treatment option.

9.3 Summary of Results

The one study included in the CADTH rapid review was conducted in 2018 by Clarke et al., in the United Kingdom as part of a larger clinical trial on rTMS.[64] The study included e-mail correspondence from 98 individuals self-referring for rTMS treatment. Across the patients who reported their demographics information, the majority were women (57.8%), 44 years of age on average (range of early 20s to mid-70s), with an average illness length of 17 years (range of four months to >40 years). The majority of the patients were depressed (88.9%) and some (20.4%) mentioned comorbidities (most often anxiety: 50%).

Thematic analysis was used to explore reasons for self-referral for rTMS treatment. Six key reasons for self-referral were identified, including current treatment not working (39.8%), proactively seeking information about treatment for depression (29.6%), suffering from chronic or long-term depression (25.5%), desperate for relief from depression (13.3%), motivated to seek alternative treatment owing to side-effects of current or previous treatment (12.2%), and getting worse in spite of current treatment regime (6.1%). The included study concluded that the reasons for self-referral were heterogenous, revealing that rTMS had broad appeal across age groups and for various reasons. The authors suggest that as rTMS becomes more widely known, it could be expected that demand for rTMS would substantially increase.

9.4 Conclusions

The findings of this review are limited due to only one study being included. There appears to be a gap in the published literature on patient experiences related to rTMS treatment provision.

10 Implementation and Budget Impact Analysis

Summary

- Three implementation scenarios for the provision of rTMS for patients with treatment-resistant depression are explored: 1) the status quo, 2) provincial funding and delivery of rTMS, and 3) provincial funding with community private delivery of rTMS, in which fee-for-service (FFS) and capitation payment models are considered.
- Estimated budget impact for the payment method in which the province pays for all components of rTMS to 11,088 patients annually are $7.3 million. To have equivalent budget impact to this payment method, weekly FFS payments would be $33.90 per patient, and monthly capitation payments would be $34.90 per patient. Estimates of FFS and capitation payments to providers are likely underestimates; with higher payments to providers resulting in greater estimated budget impact.

10.1 Purpose

To develop and consider implementation scenarios for repetitive transcranial magnetic stimulation (rTMS) in British Columbia (BC), presenting relevant evidence for each; and to estimate the comparative costs of each scenario to the publicly funded health care payer in BC over a 3-year time horizon.

10.2 Overview

Based on the evidence reported herein, three implementation scenarios were developed for consideration: 1) the status quo, 2) provincial funding and delivery of rTMS, and 3) provincial funding with community private delivery of rTMS, in which fee-for-service (FFS) and capitation payment models are considered. These scenarios were developed through an understanding of the BC context and current delivery patterns, and with consideration of the evidence presented in this HTA. This section presents the budget impact analysis, followed by the implementation considerations for each scenario.

10.3 Methods

A budget impact analysis was performed over a 3-year time horizon, corresponding to 2021, 2022, and 2023. Three implementation scenarios focusing on method of payment for rTMS were considered. Costs are considered from the perspective of the BC Ministry of Health and are presented in 2019 Canadian dollars.

[redacted]

[redacted]

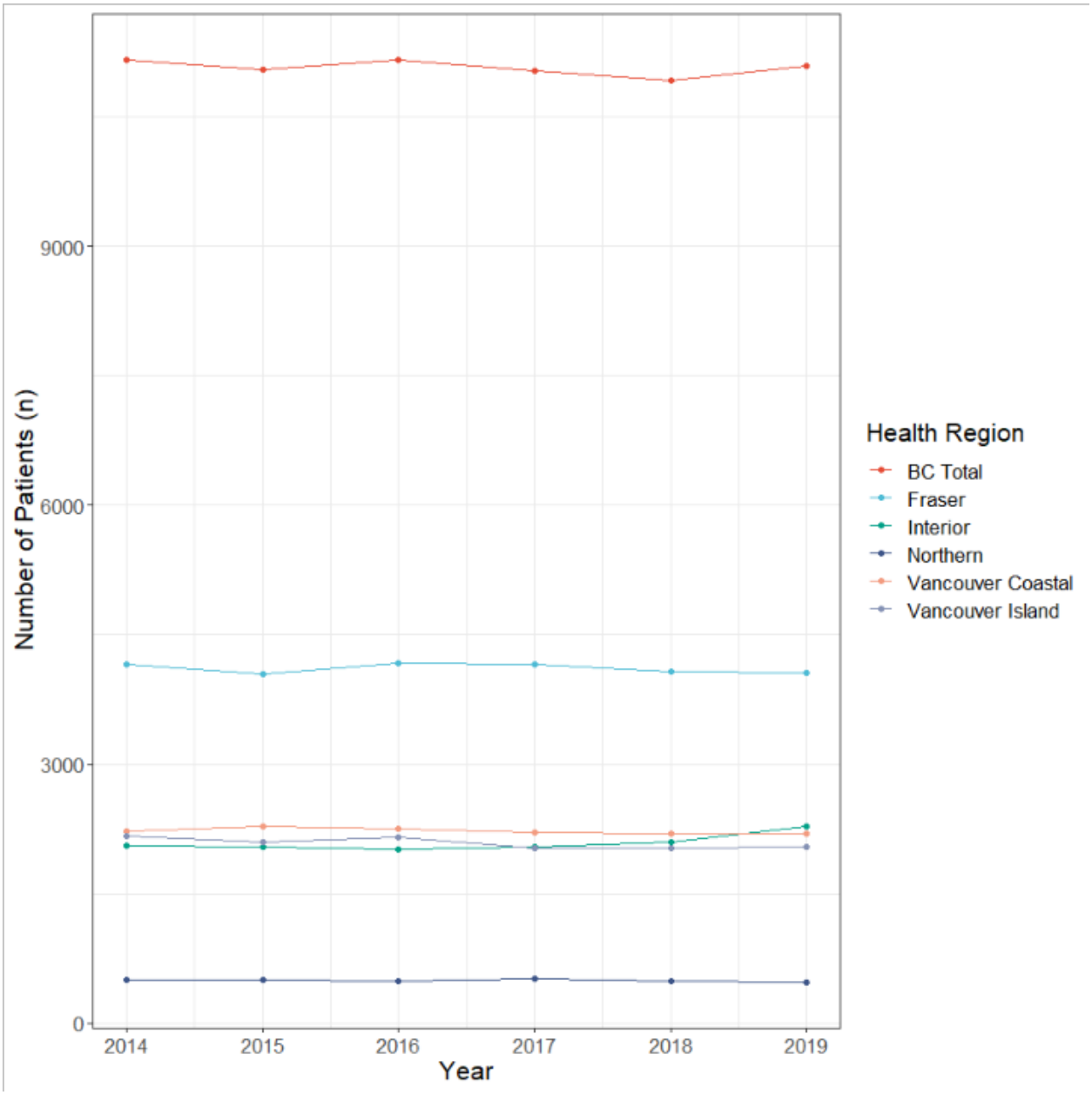
[redacted]

10.3.1 Eligible Population

The population of interest is patients with treatment-resistant depression (TRD), suitable for treatment with rTMS. To identify the number of patients with depression, an administrative data case definition validated by Doktorchik et al. (2019) was used.[65] This case definition uses the discharge abstract database and physician claims data, and requires that a patient has two physician claims with depression International Classification of Diseases codes, or one diagnosis of depression captured in the Discharge Abstract Database, within one year.[65] This algorithm has been validated and its performance has been assessed; when administrative data for 3,362 patients was compared to medical records in family physician clinics, sensitivity and specificity of this case definition were 61.4% and 94.3%, respectively.[65]

A recent systematic review by Brown et al. (2019)[46] identified the difficulty in defining "TRD". In the identified literature, more than half required a patient to have failed at least two antidepressant medications to be diagnosed with TRD.[46] From the cohort of patients with depression identified using the definition of Doktorchik et al. (2019),[65] additional criteria were applied to identify patients with TRD. To be considered TRD, patients had to have prescriptions for three or more different antidepressant medications within a year; or have prescriptions for two different antidepressant medications with no prescriptions for refills or dose adjustments within a year. It was assumed that the patients with prescriptions for two different antidepressant medications with refills or dose adjustments were seeing benefits of prescription and were therefore excluded from this definition of TRD. No exclusion criteria related to age was applied. This resulted in incidence of 11,088 patients with treatment resistant depression in 2019, who would be eligible for rTMS (Figure 13). From 2014 to 2019, the average annual change in incidence was -0.12%, thus, for this analysis, an eligible population growth rate of 0% was assumed. Growth rate of 0% reflects eligible number of patients increasing at the same rate as patients lose eligibility. The user is encouraged to modify this value in the accompanying spreadsheet.

Figure 13. Patients with TRD in BC Health Regions from 2014 to 2019



*Patients for whom health region is unknown are not pictured.

10.3.2 Scenarios

Three scenarios were considered: 1) the status quo, 2) provincial funding and delivery of rTMS, and 3) provincial funding with community private delivery of rTMS, in which fee-for-service (FFS) and capitation payment models are considered.

10.3.2.1 Scenario 1: Status Quo

Within BC, rTMS is currently available in research settings through grants, and through private clinics where the patient pays for treatment out-of-pocket. In the status quo scenario, rTMS would continue to be accessible through research settings and private clinics, and no public funds would be used for rTMS provision.

10.3.2.2 Scenario 2: Provincial Funding and Delivery of rTMS

In this scenario, the province would be responsible for funding and delivery of all components of rTMS; the province would pay the technicians that deliver treatment, provide the necessary infrastructure, and purchase rTMS machines. It is assumed that rTMS treatments could be delivered in existing healthcare facilities without additional infrastructure costs.

10.3.2.3 Scenario 3: Provincial Funding with Community Private Delivery of rTMS

In scenario 3, rTMS is publicly funded, but delivered privately within the community. Two funding models for this scenario are explored. In the first funding model, FFS, a fee is paid to rTMS providers per patient per week of treatment. In the second funding model, capitation-based payment is explored. With the capitation payment model a monthly fee is paid to the rTMS providers based on the number of patients enrolled in the practice, regardless of provision of treatment. Within both the FFS and capitation payment models, the rTMS provider would be responsible for paying technicians, rTMS machines, and procuring and maintaining any infrastructure required to deliver treatment.

10.3.3 Costs

This budget impact analysis relies heavily on cost data from an economic evaluation by Health Quality Ontario (2020); it was assumed that these costs generalize to the BC context.[66] Where costs in the Health Quality Ontario economic evaluation[66] were presented in 2019 USD, they have been converted to 2019 CAD using purchasing power parity,[67] which reflects purchasing power of currency. Following budget impact analysis best practice guidelines, no discounting is applied to this analysis.[68] Equipment costs and maintenance costs, obtained by Health Quality Ontario, are based on manufacturer suggestion, and were validated by the BC Ministry of Health.[69]

For each payment method considered, it was assumed that a psychiatric assessment, at the cost of $241.18 would be required to initiate treatment.[70] In scenario 2, where the province pays for all components of treatment, rTMS costs required the most detail. Like the economic evaluation by HQO,[66] it was assumed that the typical treatment course would include 30 acute treatments over 12 weeks, followed by 12 maintenance treatments per year. Both clinicians interviewed within this HTA (Section 8), and the Health Quality Ontario economic evaluation,[66] suggest that technicians rather than nurses would be capable of delivering rTMS therapy, once prescribed by a psychiatrist. Technicians would be paid at an hourly rate of $28.00, with 28% benefits, and would spend 15 minutes with each patient.[66] Although technicians were assumed to spend 15 minutes with each patient, clinician interviews suggested that the treatment requires 3 minutes of time with the rTMS device; with an additional two minutes to adjust and clean equipment between patients. Time spent with the rTMS device was assumed to be the rate-limiting variable for the maximum number of patients treated. It was assumed that each rTMS device would operate for 8.5 hours, 5 days per week, 52 weeks per year, and 42 rTMS treatments per patient per year; resulting in 631 patients treated per rTMS device per year.

rTMS device and coil costs, with a lifetime of five years, were converted to an equivalent annual cost, and added to annual maintenance costs. The equivalent annual cost incorporates the annual cost of capital, at a rate of 1.5% per year (selected to match the discount rate recommended by CADTH), and reflects the long-term cost of borrowing to Canadian provinces;[71] facilitating comparison with other costs in an annual budget. Because costs are calculated on an annual basis, the three-year time horizon is sufficient to capture budget impacts without making additional assumptions associated with a longer time horizon. Budget impact analysis default values are included in Table 8.

Table 8. Default Inputs in Budget Impact Analysis

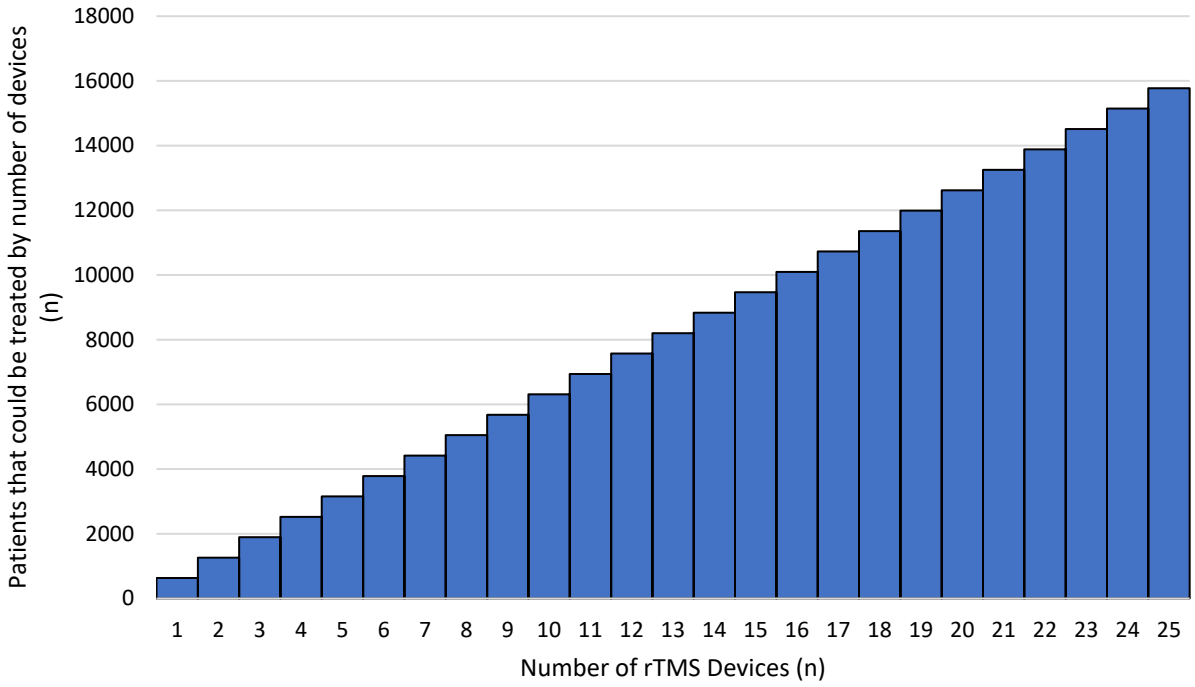
	Input Description	2019 CAD/Estimate	Source
rTMS Devices	Core equipment	$87,819.00	Manufacturer, as cited by HQO[66]
	Yearly maintenance	$3,007.50	Expert Opinion, as cited by HQO[66]
	Coil	$22,857.00	Manufacturer, as cited by HQO[66]
	Device lifetime (years)	5	Expert Opinion, as cited by HQO[66]
	Cost of capital (%)	1.5%	CADTH Economic Evaluation Guidelines[71]
	Number of devices in province in year 1	18	Calculated to cover 11,088 patients
	Additional rTMS devices in year 2	0	Assumed
	Additional rTMS devices in year 3, compared to year 2	0	Assumed
Eligible Population	Number of patients eligible to receive rTMS in 2019	11,088	BC Ministry of Health[69]
	Eligible population annual growth rate	0%	Calculated
Treatment	Physician cost to initiate rTMS	$241.18	British Columbia Medical Services Commission Payment Schedule[70]
	Length of Appointment (hours)	0.25	Expert Opinion, as cited by HQO[66]
	Technician hourly wage	$35.84	Expert Opinion, as cited by HQO[66]
	Technician cost per appointment	$8.96	Expert Opinion, as cited by HQO[66]
	rTMS device time per appointment (minutes)	5	Clinician Interviews
	Expected treatments per patient per cycle	30	Assumed, similar to HQO[66]
	Maintenance treatments per patient per year	12	Assumed, similar to HQO[66]
	Length of treatment cycle (weeks)**	12	Assumed, similar to HQO[66]
	Days per week for rTMS delivery	5	Assumed based on clinical opinion and literature
	Hours per day for rTMS delivery	8.5	Assumed

*assumes 52 weeks operation per year
**assumes 2.5 treatments per week

10.4 Results

The annual cost per rTMS device is estimated to be $26,148.67 including core equipment, coil, and annual maintenance. If each treatment cycle requires 30 treatments over 12 weeks, and 12 maintenance treatments per year, the expected cost per patient (excluding rTMS devices) is $617.50. When time spent with the rTMS device is assumed to be the rate-limiting step, each rTMS device can treat 631 patients (Figure 14).

Figure 14. Eligible Patients that Could be Treated, by Number of Devices



The results of this analysis by scenario, and year are synthesized in Table 9. Implementation considerations are synthesized in Table 10.

Table 9. Estimated Budget Impact over Three Years

	Predicted Budget Impact			
	Year 1	**Year 2**	**Year 3**	**Total**
Scenario 1: Status quo • rTMS is not publicly funded by the province.	$0	$0	$0	$0
Scenario 2: Provincial funding and delivery of rTMS funded by the province.	$7,317,516	$7,317,516	$7,317,516	$21,952,548
Scenario 3: Provincial funding with community private delivery of rTMS.	$7,317,858	$7,317,858	$7,317,858	$21,953,575

*FFS paid per patient per week is $33.90; Capitation fee paid per patient per month is $34.90.

Table 10. Implementation Considerations

	Status Quo (Scenario 1) *Continue to Only Offer rTMS Through Research and Private Clinics*	**Provincial Funding and Delivery of rTMS (Scenario 2)**	**Provincial Funding with Community Private Delivery of rTMS (Scenario 3)**
Condition Severity	• Depression is a common mood disorder that affects a person's psychological, physical, interpersonal, and occupational functioning. • Less than 50% respond to first-line treatment of psychotherapy or antidepressants, resulting in treatment-resistant depression (TRD) • TRD is characterized by substantial functional impairment, as well as direct and indirect costs to the health system and the workforce.		
Health Benefits/Drawbacks	• Limited health benefits due to very few people being able to access rTMS. • A meta-analysis conducted by the HTA Unit in 2014 found rTMS to be an effective treatment for TRD; rTMS was associated with significantly higher response (RR=2.35, 95% CI: 1.70-3.25) and higher remission (RR=2.24, 95% CI: 1.53-3.27); rTMS was statistically similar to ECT with respect to response (RR=1.09, 95% CI: 0.79-1.48) and remission (RR=0.97, 95% CI: 0.65-1.45).[7] • The systematic review of safety conducted by the HTA Unit in 2014 found that the most frequently reported adverse effects in studies comparing rTMS to sham were pain/discomfort and headache. Headaches were reported to occur in both the rTMS and sham groups (up to 60% for rTMS versus up to 50% for sham) and to subside quickly. Similarly, discomfort and pain were generally reported in both the rTMS and sham groups. Across the six studies comparing rTMS to ECT, pain/discomfort and headache were the most common symptoms. None of the studies comparing rTMS to sham or	• A meta-analysis conducted by the HTA Unit in 2014 found rTMS to be an effective treatment for TRD; rTMS was associated with significantly higher response (RR=2.35, 95% CI: 1.70-3.25) and higher remission (RR=2.24, 95% CI: 1.53-3.27); rTMS was statistically similar to ECT with respect to response (RR=1.09, 95% CI: 0.79-1.48) and remission (RR=0.97, 95% CI: 0.65-1.45).[7] • The systematic review of safety conducted by the HTA Unit in 2014 found that the most frequently reported adverse effects in studies comparing rTMS to sham were pain/discomfort and headache. Headaches were reported to occur in both the rTMS and sham groups (up to 60% for rTMS versus up to 50% for sham) and to subside quickly. Similarly, discomfort and pain were generally reported in both the rTMS and sham groups. Across the six studies comparing rTMS to ECT, pain/discomfort and headache were the most common symptoms. None of the studies comparing rTMS to sham or rTMS to ECT reported serious adverse events, such as cognitive impairment, seizure, or suicidal ideation.[7] • Interviewed health care providers report that rTMS is an effective treatment for TRD. • CANMAT guidelines on neurostimulation or neuromodulation treatments for treatment of depression recommend rTMS as the first-line treatment for individuals with TRD (i.e., patients with depression who have failed at least one trial of antidepressant treatment). • Interviewed health care providers reported that rTMS has minor side effects but that these typically disappear within a few hours of the treatment session and have not been observed to be a deterrent to patients.	

	Status Quo (Scenario 1) *Continue to Only Offer rTMS Through Research and Private Clinics*	**Provincial Funding and Delivery of rTMS (Scenario 2)**	**Provincial Funding with Community Private Delivery of rTMS (Scenario 3)**
	rTMS to ECT reported serious adverse events, such as cognitive impairment, seizure, or suicidal ideation.[7]		
Non-Health Benefits/Drawbacks	• Limited non-health benefits due to very few people being able to access rTMS.	• Interviewed health care providers described their patients with TRD who were able to go back to work and be involved in caring for their children because of rTMS treatment	
Ethical Considerations	• Patients would continue to have limited access to alternative treatment options to antidepressants and ECT. • Does not align with rTMS access in Alberta, Saskatchewan, and Quebec, where rTMS is publicly funded.	• Patients would have alternative treatment options to antidepressants and ECT. • Would align with rTMS access in Alberta, Saskatchewan, and Quebec, where rTMS is publicly funded. • Aligns with CANMAT guidelines on neurostimulation or neuromodulation treatments for treatment of depression.	• Patients would have alternative treatment options to antidepressants and ECT. • Would align with rTMS access in Alberta, Saskatchewan, and Quebec, where rTMS is publicly funded. • Aligns with CANMAT guidelines on neurostimulation or neuromodulation treatments for treatment of depression. • Assuming the provider's goal is to maximize income, an FFS payment model may incentivize increased care provision. As such, FFS payment may result in unnecessary use, especially if rTMS is prescribed and provided by the same physician. • To maximize income under a capitation payment model, providers are incentivized to increase enrollment in their practice, and minimize costs of providing care. This may entice rTMS providers to enroll patients that achieve remission, and to avoid providing care for patients that require ongoing or repeat treatments to achieve response.

	Status Quo (Scenario 1) *Continue to Only Offer rTMS Through Research and Private Clinics*	**Provincial Funding and Delivery of rTMS (Scenario 2)**	**Provincial Funding with Community Private Delivery of rTMS (Scenario 3)**
Underserved Populations	• Interviewed health care providers feel that there is a treatment gap in BC for patients with TRD who have not responded to antidepressants, cannot tolerate their side effects, are not ill enough to require ECT, or are unable to access it; status quo would result in this patient population continuing to have limited access to rTMS. • Current access to rTMS is inequitable across the province (e.g., delivered in Victoria and Vancouver only). • The cost of rTMS in private clinics is prohibitive to some patients (particularly low SES and other vulnerable populations). • Free rTMS treatment delivered as part of a research study has a long waitlist. • The cost of accommodations for patients living outside of driving distance to current rTMS treatment centres is prohibitive to some patients (particularly low SES and other vulnerable populations).	• Interviewed health care providers feel that rTMS would fill a treatment gap for BC patients with TRD who have not responded to antidepressants, cannot tolerate their side effects, are not ill enough to require ECT, or are unable to access it. • Patients with TRD were reported to be very interested in rTMS as an alternative treatment option to antidepressants and ECT. • If funded and delivered by the province, location of care provision could be matched to patient need, specifically targeting underserved populations and promoting equity. • Depending on the locations of the rTMS treatment centres, access may be inequitable across the province (e.g., delivering rTMS in urban centres only would mean inequitable access for patients living in rural and remote locations). • Patients (particularly low SES and other vulnerable populations) living outside of driving distance of the rTMS treatment centres may be unable to afford to pay for out-of-pocket for accommodation.	• Inequitable access may continue, as providers determined where to establish clinics. Geographically isolated locations would likely lack sufficient demand for single providers to establish sustainable clinics. • Depending on the locations of the rTMS treatment centres, access may be inequitable across the province (e.g., delivering rTMS in urban centres only would mean inequitable access for patients living in rural and remote locations). • Patients (particularly low SES and other vulnerable populations) living outside of driving distance of the rTMS treatment centres may be unable to afford to pay for out-of-pocket for accommodation.
Evidence of Cost-Effectiveness	• The cost-effectiveness analysis conducted by the HTA Unit in 2014 found that rTMS was more costly and more effective than sham at achieving response and remission with a cost per QALY gained of $13,084 and $20,203, respectively.[7] • rTMS was found to be less expensive and more effective than ECT at achieving response, and less expensive and more effective at achieving remission (ECT had a cost per QALY gained of $328,325 compared to rTMS).[7]		

	Status Quo (Scenario 1) *Continue to Only Offer rTMS Through Research and Private Clinics*	**Provincial Funding and Delivery of rTMS (Scenario 2)**	**Provincial Funding with Community Private Delivery of rTMS (Scenario 3)**
Environmental Impact	• Unknown environmental impact. Considerations may include daily driving distance to the treatment centre, and the environmental impact of manufacturing the rTMS machine and accessories (e.g., coils).		
Implementation Considerations	• None; no change.	• Interviewed health care providers feel that administering rTMS under provincial funding, rather than other funding models, may limit access because it would confine the treatment to select settings (e.g., hospitals). • Delivering rTMS in hospitals would require displacement of other hospital services, which would require additional funding for the displaced services. • Patients may require rTMS maintenance treatment, which may limit access to treatment for new patients. • Interviewed health care providers reported on emerging research for additional indications for rTMS (e.g., obsessive-compulsive disorder); access could be expanded to other indications in the future.	• Interviewed health care providers report that funding rTMS in community settings would increase access to patients but may require additional resources to establish quality control procedures to ensure standard of care across the province. • Delivering rTMS in community settings that already have psychiatrists on a sessional basis would not require displacement of hospital resources. • Interviewed health care providers reported on emerging research for additional indications for rTMS (e.g., obsessive-compulsive disorder); access could be expanded to other indications in the future. • Patients may require rTMS maintenance treatment, which may limit access to treatment for new patients.
Risk Registry: Financial	• The estimated budget impact of maintaining the status quo is $0, and unchanged.	• The estimated budget impact of provincial funding of rTMS is $7.3 million per year, for a total estimated budget impact of nearly $21.9 million over three years • Low-cost accommodations may need to be considered for patients not living within driving distance of an rTMS centre.	• To have the same budget impact as a provincial funding and delivery model, the fee paid per patient per week in an FFS model would be $33.90; and in a capitation-based payment model, $34.90 per patient per month. These estimates of fees paid to service providers are likely too low to entice care provision across

	Status Quo (Scenario 1) *Continue to Only Offer rTMS Through Research and Private Clinics*	**Provincial Funding and Delivery of rTMS (Scenario 2)**	**Provincial Funding with Community Private Delivery of rTMS (Scenario 3)**
			the province and may result in underservice of this patient population. • With a FFS payment model, the province would have little control over total cost, as providers bill for any volume without restriction. With a capitation payment model, the province may have greater ability to cap total annual cost by patient enrollment per practice. • Low-cost accommodations may need to be considered for patients not living within driving distance of an rTMS centre.
Risk Registry: Human Resources	• None; no change.	• Province would be responsible for recruiting and training rTMS technicians who would deliver rTMS and physicians who would oversee the treatment.	• Individual clinics would be responsible for recruiting and training rTMS technicians who would deliver rTMS and physicians who would oversee the treatment.

10.4.1 Scenario 1: Status Quo

The expected budget impact of maintaining the status quo (continuing to deliver rTMS in private clinics and research settings only) over the next three years is zero and unchanged.

This scenario, where rTMS remains limited to private clinics or research settings with long waitlists, is not supported by a meta-analysis of the clinical observational literature conducted by the HTA Unit in 2014, which found rTMS to be superior to sham in terms of health-related outcomes. Since rTMS is currently only offered in Victoria and Vancouver, access to rTMS in this scenario would continue to be inequitable based on geographic location and ability to pay for treatment.

This scenario does not align with the perspectives of BC health care providers who feel that BC has a treatment gap for patients with TRD who have not responded to antidepressants, cannot tolerate their side effects, are not ill enough to require ECT, or are unable to access it. These patients will continue to have a limited number of alternative treatment options to antidepressants. Furthermore, the cost of rTMS treatment at private clinics and the cost of accommodations for patients not living within driving distance of an rTMS centre will continue to prohibit access to some patients (e.g., low SES and other vulnerable populations). Currently, only one clinic in BC (in Vancouver) offers free rTMS treatment as part of a research study but the wait times are long; wait times will remain unchanged in this scenario.

This scenario does not align with the results of a cost-effectiveness analysis conducted by the HTA Unit in 2014, which found that rTMS was more effective and less expensive than sham at achieving response and remission. It also does not align with rTMS access in Alberta, Saskatchewan, and Quebec, where rTMS is publicly funded.

10.4.2 Scenario 2: Provincial Funding and Delivery of rTMS

To treat all eligible patients in the first year, assuming rTMS machines operate 5 days per week, 8.5 hours per day, with 5 minutes of device time per patient, and 42 treatments required per patient per year, 18 rTMS devices would be required (Table 11). To provide rTMS to all patients

with TRD is estimated to cost $7.3 million per year, for a total estimated budget impact of $21.9 million over three years.

Table 11. Number of Eligible Patients that Could be Cared for with 18 Devices when Province Pays for All Components of Care Separately

			Year 1	Year 2	Year 3
Year	**2019**	**2020 (predicted)**	**2021 (predicted)**	**2022 (predicted)**	**2023 (predicted)**
Number of eligible patients	11,088	11,088	11,088	11,088	11,088
Number of eligible patients that could be cared for with number of devices*			11,088	11,088	11,088
Percent of eligible patients that could receive rTMS with number of devices*			100%	100%	100%
Percent of eligible patients that would not receive rTMS with number of devices*			0%	0%	0%

*eligible patients that could be cared for with number of devices only applies to scenario 2, where province pays for all components of treatment

This scenario is supported by a meta-analysis of the clinical observational literature conducted by the HTA Unit in 2014, which found rTMS twice as likely to result in response and remission when compared to sham. It also aligns with CANMAT guideline recommendations for rTMS as a first-line treatment for patients with TRD and BC health care providers' perceptions of rTMS as an effective treatment for this population. Interviewed BC health care providers felt that rTMS treatment side effects are minor and have not been observed to be a deterrent to patients. Non-health benefits of rTMS observed by interviewed health care providers in their patients included the ability to go back to work and be involved in childcare following treatment.

This scenario aligns with the perspectives of BC health care providers who feel that BC has a treatment gap for patients with TRD who have not responded to antidepressants, cannot tolerate their side effects, are not ill enough to require ECT, or are unable to access it. Health care providers also felt that patients are very interested in rTMS as a treatment option. In this scenario, patients with TRD would have alternative treatment options to antidepressants and ECT. The province would determine locations of rTMS provision and could match the location of patient need and promote equity. However, depending on the locations of rTMS treatment centres, access to rTMS may continue to be inequitable across the province (i.e., implementing rTMS in urban centres would mean inequitable access for patients living in rural and remote parts of BC). Furthermore, the out-of-pocket cost of accommodations for patients living outside of driving distance of an rTMS centre may continue to be prohibitive to some patients (e.g., low SES and other vulnerable populations). Low-cost accommodations may need to be considered for these patients.

Interviewed health care providers felt that funding rTMS under this implementation scenario may potentially limit access to rTMS because it would confine the treatment to select settings (e.g., in-hospital provision only). It should also be considered that patients who had undergone a course of rTMS may require maintenance treatment, which may limit access to new patients. Lastly, interviewed health care providers felt that emerging research on additional rTMS indications (e.g., obsessive compulsive disorder) may lead to expanding access to other indications in the future.

This scenario aligns with the results of a cost-effectiveness analysis conducted by the HTA Unit in 2014, which found that rTMS was more effective and more costly compared to sham, with a cost per QALY gained of $13,084. It also aligns with rTMS access in Alberta, Saskatchewan, and Quebec, where rTMS is publicly funded. In this scenario, the province of BC would be responsible for recruiting and training rTMS technicians who would deliver the treatments and physicians who would oversee the treatment process. If funded and delivered by the province, location of care provision could be matched to patient need, specifically targeting underserved populations, and promoting equity.

10.4.3 Scenario 3: Provincial Funding with Community Private Delivery of rTMS

In this scenario, costs of rTMS machines were not considered because rTMS providers would be responsible for providing rTMS machines and paying technicians to operate them. For the FFS payment method to have the same estimated budget impact as the fee paid to providers per patient per week of treatment, the fee paid would be $33.90. Similarly, under a capitation payment method, the monthly fee paid to rTMS providers would be $34.90 (Table 9). Providing rTMS to all patients with treatment resistant depression is estimated to cost $7.3 million per year, for a total estimated budget impact of $21.9 million over three years. Although FFS and capitation costs were calculated to be equivalent to the cost of provincial funding and delivery of rTMS, these estimates of fees are likely not realistic values. Profit for providers was not considered, and the estimates of fees paid to service providers are likely too low to entice care provision across the province; and may result in underservice of this patient population. With the FFS and capitation payments used, this scenario reflects the cost of patient care with variation on the funding model. The user is encouraged to adjust these values to explore the total budget impact of differing provider payment amounts.

This scenario is supported by meta-analysis of the clinical observational literature conducted by the HTA Unit in 2014, which found rTMS twice as likely to result in response and remission when compared to sham. This scenario also aligns with CANMAT guideline recommendations for rTMS as a first-line treatment for patients with TRD and BC health care providers' perceptions of rTMS as an effective treatment for this population. Interviewed BC health care providers felt that rTMS treatment side effects are minor and have not been observed to be a deterrent to patients. Non-health benefits of rTMS observed by interviewed health care providers in their patients included the ability to go back to work and be involved in childcare following treatment.

This scenario aligns with the perspectives of BC health care providers who feel that BC has a treatment gap for patients with TRD who have not responded to antidepressants, cannot tolerate their side effects, are not ill enough to require ECT, or are unable to access it. Health care providers also felt that patients are very interested in rTMS as a treatment option. In this scenario, patients with TRD would have alternative treatment options to antidepressants and

ECT. However, depending on the locations of rTMS treatment centres, access to rTMS may continue to be inequitable across the province (i.e., implementing rTMS in urban centres would mean inequitable access for patients living in rural and remote parts of BC). Inequitable access to rTMS may continue, as providers determine where to establish clinics. Geographically isolated locations would likely lack sufficient demand for providers to establish sustainable clinics. Furthermore, the out-of-pocket cost of accommodations for patients living outside of driving distance of an rTMS centre may continue to be prohibitive to some patients (e.g., low SES and other vulnerable populations). Low-cost accommodations may need to be considered for these patients.

Interviewed health care providers felt that funding rTMS in community settings under an FFS or a capitation model would increase access to patients but may require additional resources to establish quality control procedures to ensure standard of care across the province. It should also be considered that patients who had undergone a course of rTMS may require maintenance treatment, which may limit access to new patients. Lastly, interviewed health care providers felt that emerging research on additional rTMS indications (e.g., obsessive compulsive disorder) may lead to expanding access to other indications in the future.

This scenario aligns with the results of a cost-effectiveness analysis conducted by the HTA Unit in 2014, which found that rTMS was more effective and more costly compared to sham, with a cost per QALY gained of $13,084. They also align with rTMS access in Alberta, Saskatchewan, and Quebec, where rTMS is publicly funded. In these scenarios, individual clinics would be responsible for recruiting and training rTMS technicians who would deliver the treatments and physicians who would oversee the treatment process.

10.5 Conclusions

This budget impact analysis considers three scenarios that assess the potential impact of publicly funded rTMS in BC.

Since rTMS is currently accessible only through research settings and private clinics, scenario 1, which models the status quo and reflects no public funding of rTMS, would result in zero

expenditure. This scenario is not supported by the literature which suggests that rTMS is more efficacious than sham in terms of health-related outcomes and does not align with current CANMAT recommendations. In this scenario, inequities based on geographic location and ability to pay for treatment would persist. This scenario does not align with the perspectives of BC health care providers, who felt that there is a current treatment gap for patients in BC.

In scenario 2, where rTMS is funded and delivered by the province, the estimated budget impact to provide rTMS to 11,088 patients is $7.3 million per year, for a total of $21.9 million over three years. This scenario is supported by the literature which suggests that rTMS is more efficacious than sham in terms of health-related outcomes; and aligns with CANMAT recommendations. It also aligns with the perspectives of BC health care providers who feel there is a treatment gap for patients with TRD. In this scenario, access to rTMS could be more equitable, depending on location of treatment centers; geographic inequity may or may not persist. Health care providers described both benefits (e.g. standardized care) and drawbacks (e.g. potentially limiting access to select settings) of this funding model.

In scenario 3, in which the province funds rTMS but therapy is delivered in a private community setting, FFS and capitation models were considered. Weekly FFS payments would be $33.90, or monthly capitation payments would be $34.90, to have the same budget impact as scenario 2. The third scenario is also supported by the literature, which suggests that rTMS is more efficacious than sham in terms of health-related outcomes; and aligns with CANMAT recommendations. They align with the perspectives of BC health care providers who feel there is a treatment gap for patients with TRD. Both the FFS and capitation payment models may result in geographic inequity in care provision. Because care providers would determine locations with rTMS availability, geographically isolated locations lacking sufficient demand are unlikely to have care providers establish treatment centers. Health care providers described both benefits (e.g. potentially increased access) and drawbacks (e.g. potential lack of treatment standardization) of community-delivered funding models.

10.5.1 Limitations

Estimates of eligible population size are not exact. To identify patients with major depressive disorder, a case definition with sensitivity and specificity of 61.4% and 94.3%, respectively, was used.[65] The false negative rate, calculated as 1 minus sensitivity, is nearly 40%; suggesting that the population prevalence of major depressive disorder has been underestimated. The literature lacks consensus on the definition of TRD.[46] Without a validation study, it is unknown how the applied definition of TRD has affected the number of eligible patients. Therefore, the number of eligible patients is an approximation.

Although efficacy of rTMS is excellent, response to treatment is not universal. In one systematic review and meta-analysis of randomized controlled trials estimated the effect of rTMS on patients with TRD, 29.3% of patients responded to treatment and 18.6% of patients achieved remission.[72] If rTMS were to be funded for only those patients that responded to treatment, or achieved remission, fewer rTMS devices would be needed and the estimated budget impact would be lower. If provided for 29.3% (n = 3,249) of patients, the annual estimated budget impact would be $2.1 million with 6 rTMS devices; and if provided for 18.6% (n = 2,062) of patients, the annual estimated budget impact would be $1.4 million with 4 rTMS devices. In this analysis, perfect coverage and 100% utilization of rTMS devices was assumed. No assumptions about locations of rTMS machines in relation to eligible patients were made. It is likely that additional rTMS machines would be required to provide care to patients living in remote geographic locations.

Although FFS and capitation payments were calculated to show budget impact equivalent to a provincially funded and delivered scenario, these payment values are likely not realistic. Payment values reflect the cost of care provision, and do not incorporate a salary or profit for the owner of the rTMS device. In Saskatchewan, although rTMS is not provincially funded, the Saskatchewan Medical Association guide to uninsured services suggests fees of $163 for the technical component of rTMS, in addition to professional fees of $104 for necessary treatment, and $86.20 per quarter hour of continuous personal attendance.[73] In Alberta, the fee for 15 minutes of a psychiatrist's time is $47.54.[74] In BC, the FFS paid to a psychiatrist for an office visit, to include services such as minimal psychotherapy, is $54.21.[70] Recognizing that none of

these fee suggestions generalizes to the proposed provincial funding of rTMS context in BC, both serve to illustrate that a FFS payment of $33.90 or a capitation payment of $34.90 is likely too low. These values represent the cost of patient care. The difference between these payment values and higher FFS or capitation payments is the profit that a provider might earn. By setting these values at cost equivalence, the province may estimate the proportion of FFS or capitation payments that goes to patient care, and the proportion that is provider profit. To increase profits, providers may also provide care for additional patients, in additional hours, or additional days per week. The user is encouraged to adjust these values in the accompanying spreadsheet.

10.5.2 Funding Model Considerations

Different methods of payment for physicians, which can be generalized to rTMS providers, have differing incentives and consequences. Ideally, the method of payment would improve quality and access to care, reduce unnecessary care, and simultaneously promote physician and patient satisfaction.[75] Assuming the provider's goal is to maximize income, a FFS payment model may incentivize increased care provision. As such, FFS payment may result in unnecessary use, especially if rTMS is prescribed and provided by the same physician. Compared to capitation, FFS payment has been associated with increased patient and provider satisfaction, improved patient outcomes, and higher use of services.[75,76]

To maximize income under a capitation payment model, providers are incentivized to increase enrollment in their practice, and minimize costs of providing care. This may entice rTMS providers to enroll patients that achieve remission, and to avoid providing care for patients that require ongoing or repeat treatments to achieve response. Replacing FFS with capitation payment models has been associated with decreases in elective procedures, and increased use of less costly procedures.[76] Evidence regarding access to care under capitation versus FFS is mixed, although unintended consequences include reduced patient and physician satisfaction with capitation, and little difference in quality of care.[75]

If rTMS is implemented with FFS payments to providers, the province would have little control over total cost, as providers are able to bill for any volume without restriction. With a capitation

payment model, the province may have greater ability to cap total annual cost by patient enrollment per practice.

Quinn et al. (2020)[76] suggests that effects of payment models for physicians differ depending on context. Outcomes observed with implementation of rTMS under any funding model suggested may differ from previously observed incentives and clinical outcomes. However, funding of rTMS in any capacity in BC presents an opportunity to explore the effect of differing payment methods on usage, cost, patient outcomes, and provider outcomes.

11 Report Conclusions

This report presents the findings and conclusions of a provincial HTA on the use of rTMS for TRD. It builds off of an HTA previously completed with the University of Calgary HTA Unit[7] which found robust evidence of superiority of rTMS compared to sham for treatment of TRD for response and remission, with rTMS being more effective and less expensive than sham at achieving response and remission. Considered within the present HTA is evidence from patients, and clinicians, a survey of rTMS delivery practices across Canada, a systematic review of implementation models, and an implementation and budget impact analysis; all focused on the implementation of rTMS.

The survey of Canadian rTMS providers found that rTMS is publicly funded in Alberta, Saskatchewan, and Quebec; patients in Ontario are also reported to receive rTMS free of charge with costs covered by philanthropic, hospital, or research funds. This is consistent with current Canadian guidelines, which recommend rTMS as a first-line treatment after failing at least one trial of antidepressants. Across Canada, rTMS was delivered in outpatient clinics, research studies, and private clinics. It was reported that training for rTMS was provided by the Canadian rTMS distributor, by the Centre for Addictions and Mental Health, and internally by other staff trained in rTMS delivery.

The systematic review of rTMS implementation models broadly found four themes from six studies: assessment and safety, treatment room design, patient comfort, and psychoeducation. Literature described how the parameters for rTMS treatment should be determined by a psychiatrist; however, treatment could be delivered by nurses or technicians under supervision. Given their involvement in all stages of the treatment process, the creation of a trusting nurse-patient relationship substantially impacted patient's experiences with rTMS treatment. Studies reported enhancing treatment room comfort by adding a comfortable chair and pillows, muted wall colours, artwork featuring nature, and relaxing music. Safety precautions included hearing protection for the patients and operator, first responder training, and emergency response protocols.

The seven health care providers interviewed felt unanimously that rTMS should be publicly funded for people with TRD. BC has a treatment gap for patients with TRD who have not responded to or are intolerant of antidepressants and for whom ECT is not an option. rTMS was perceived to be well-positioned to bridge the treatment gap for these patients, given the established body of effectiveness literature and relative ease of administration. Health care providers perceived rTMS to be cheaper than ECT, and all agreed that there was patient demand for rTMS as an alternative treatment option to medications and/or ECT. Access to rTMS in BC was reported to be inequitable, as it is currently only offered in a few clinics in Victoria and the Vancouver region. Current access was perceived to be further limited by the high cost of the treatment, the need to pay for accommodations out-of-pocket, and the time commitment associated with daily treatment administration for working individuals.

The rapid review of qualitative literature conducted by CADTH identified one study for inclusion. The included study explored the reasons for self-referral, which included: current treatment not working, proactively seeking information about treatment for depression, suffering from chronic or long-term depression, desperate for relief from depression, motivated to seek alternative treatment owing to side-effects of current or previous treatment, and getting worse in spite of current treatment regime. The included study concluded that the reasons for self-referral were heterogenous, revealing that rTMS had broad appeal across age groups and for various reasons. Broadly, this rapid review highlights a gap in patient perspective literature.

Based on the evidence presented herein, three implementation scenarios for the provision of rTMS for patients with TRD were explored: 1) maintain status quo where rTMS is not publicly funded, 2) the province pays for and delivers all components of rTMS, and 3) a community-delivered model in which rTMS providers are paid by fee for service or capitation. The budget impact analysis found that over the next three years, to provide treatment to 11,088 patients, the cost of maintaining the status quo is $0, and provincial funding and delivery of rTMs would result in an expenditure of $7.3 million per year. If rTMS were publicly funded and community delivered, a fee for service model or capitation model could be adopted. To have the same budget impact as scenario 2, weekly fee for service payments would be $33.90 or monthly capitation

payments would be $34.90. Each scenario has unique advantages and disadvantages including impact on health and non-health benefits, provincial expenditure, and access equity.

Ethical considerations for implementing rTMS for treatment of TRD in BC centred around treatment access, financial incentives to care providers, and alignment of care with other Canadian jurisdictions. Status quo (continue to only offer rTMS privately and through a research study) would mean patients with TRD continuing to have limited access to alternative treatment options to antidepressants and ECT. This scenario would also not align with rTMS access in Alberta, Saskatchewan, and Quebec, where rTMS is publicly funded. Provincial funding of rTMS with or without community private care delivery would allow BC patients to have access to alternative treatment options, which is something that the BC health care providers strongly advocated for and believed patients want. These scenarios would also align with care recommended by the CANMAT guidelines for treatment of TRD and align with rTMS access in the three provinces where rTMS is publicly funded. However, the capitation payment model may entice rTMS providers to enroll patients that achieve remission and to avoid providing care for patients that require ongoing or repeat treatments to achieve response; whereas FFS may incentivize increased care provision and result in unnecessary use, especially if rTMS is prescribed and provided by the same physician.

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13 Appendix A

Survey of Canadian rTMS Providers

Setting and Service Provision

1. Approximately how many patients with depression do you treat with rTMS each year (maintenance and new)?
2. In what settings is rTMS offered in your province (e.g. acute care, primary care, research study?)
3. How many machines do you have? What types?
4. What is the staffing model at your clinic (i.e., who typically delivers rTMS treatment)? And what training is provided to technicians administering rTMS?

Costs

5. How is rTMS currently funded at your facility? Is there a cost to patients?
6. What, if any, assistance is provided by the province or by your clinic to help patients undergoing rTMS (e.g., facilitate finding accommodation, other patient resources)?

14 Appendix B

Systematic Review Search Strategy

Cochrane CENTRAL Register (OVID)

1. rtms.tw
2. ((repeat* or repetiti*) adj3 tms).tw.
3. ((repeat* or repetiti*) adj3 (transcranial adj3 magnetic adj3 stimulation*)).tw.
4. 1 or 2 or 3
5. exp Transcranial Magnetic Stimulation/ec, st, sn, ut [Economics, Standards, Statistics & Numerical Data, Utilization]
6. health planning/ or health plan implementation/
7. "process assessment (health care)"/ or exp program evaluation/ or exp "utilization review"/ or "delivery of health care"/
8. exp "organization and administration"/ or waiting lists/ or decision making, organizational/ or eligibility determination/
9. exp Inservice Training/
10. education, medical/ or education, medical, continuing/
11. exp Clinical Protocols/
12. patient identification systems/ or "personnel staffing and scheduling"/
13. Referral and Consultation"/
14. (administer* or administration or coordinating or coordination or implement* or management or managing or operation* or organi* or performance or planning).tw.
15. (education or protocol* or staffing or train or training).tw.
16. (care adj1 model*).tw.
17. (funded or funding or referral* or wait* list*).tw.
18. (patient* adj selec*).tw.
19. (assess* or evaluat*).tw.
20. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 4 and 20
22. limit 21 to (english or french)
23. limit 22 to animals
24. limit 22 to (animals and humans)
25. 23 not 24
26. 22 not 25
27. Limit 26 to (editorial or letter)
28. 26 not 27

EMBASE (OVID)

1. rtms.tw.
2. ((repeat* or repetiti*) adj3 tms).tw.
3. ((repeat* or repetiti*) adj3 (transcranial adj3 magnetic adj3 stimulation*)).tw.
4. exp repetitive transcranial magnetic stimulation/
5. 1 or 2 or 3 or 4
6. health care planning/
7. "organization and management"/

8. manpower planning/ or patient care planning/ or program development/ or strategic planning/
9. management/ or manpower/ or patient identification/ or personnel management/ or resource management/ or time management/ or work schedule/ or workflow/
10. exp program evaluation/
11. exp "utilization review"/
12. health care delivery/
13. exp in service training/
14. exp medical education/
15. exp clinical protocol/
16. exp nursing staff/ or exp manpower/ or exp personnel management/
17. accident prevention/ or patient safety/
18. exp patient scheduling/
19. exp patient referral/
20. (administer* or administration or coordinating or coordination or implement* or management or managing or operation* or organi* or performance or planning).tw.
21. (education or protocol* or staffing or train or training).tw.
22. (care adj1 model*).tw.
23. (funded or funding or referral* or wait* list*).tw.
24. (patient* adj selec*).tw.
25. (assess* or evaluat*).tw.
26. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 5 and 26
28. limit 27 to animal studies
29. limit 27 to (human and animal studies)
30. 28 not 29
31. 27 not 30
32. limit 31 to (english or french)
33. limit 32 to (editorial or letter)
34. 32 not 33
35. limit 34 to conference abstract
36. 34 not 35

PsycINFO (OVID)
1. rtms.tw.
2. ((repeat* or repetiti*) adj3 tms).tw.
3. ((repeat* or repetiti*) adj3 (transcranial adj3 magnetic adj3 stimulation*)).tw.
4. 1 or 2 or 3
5. exp Treatment Planning/
6. educational programs/
7. exp program evaluation/
8. program development/ or curriculum development/ or exp educational programs/ or exp hospital programs/ or exp mental health programs/ or exp program evaluation/ or exp psychiatric hospital programs/
9. exp Utilization Reviews/
10. exp Health Care Utilization/ or exp Health Care Delivery/

11. exp HOSPITAL ADMINISTRATION/ or exp HEALTH CARE ADMINISTRATION/ or exp TEST ADMINISTRATION/
12. exp management decision making/ or decision making/
13. patient selection/
14. client characteristics/
15. inservice training/ or continuing education/ or personnel training/ or mental health inservice training/
16. exp Medical Education/
17. exp Treatment Guidelines/
18. exp Medical Personnel/ or exp Mental Health Personnel/ or exp Personnel Selection/ or exp Personnel Recruitment/
19. professional referral/ or client transfer/ or self-referral/
20. (administer* or administration or coordinating or coordination or implement* or management or managing or operation* or organi* or performance or planning).tw.
21. (care adj1 model*).tw.
22. (funded or funding or referral* or wait* list*).tw.
23. (patient* adj selec*).tw.
24. (assess* or evaluat*).tw.
25. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 4 and 25
27. limit 26 to animal
28. limit 26 to (animal and human)
29. 27 not 28
30. 26 not 29
31. limit 30 to (english or french)
32. limit 31 to (editorial or letter)
33. 31 not 32

Cochrane Database of Systematic Reviews (OVID)
HTA Database (OVID)
1. rtms.tw.
2. ((repeat* or repetiti*) adj3 tms).tw.
3. ((repeat* or repetiti*) adj3 (transcranial adj3 magnetic adj3 stimulation*)).tw.
4. 1 or 2 or 3
5. (administer* or administration or coordinating or coordination or implement* or management or managing or operation* or organi* or performance or planning).tw.
6. (education or protocol* or staffing or train or training).tw.
7. (care adj1 model*).tw.
8. (funded or funding or referral* or wait* list*).tw.
9. (patient* adj selec*).tw.
10. (assess* or evaluat*).tw.
11. 5 or 6 or 7 or 8 or 9 or 10
12. 4 and 11

15 Appendix C

Clinician Interview Guide

Preamble: *As you know, the University of Calgary Health Technology Assessment Unit is speaking with clinicians about their experiences with rTMS for treatment resistant depression as part of the background research for a Health Technology Assessment for the BC Ministry of Health. The interview will take about 45-60 minutes (depending on your responses) and, with your permission, will be audio-recorded for accuracy. Do you have any questions before we begin?*

About you and your experience with rTMS

1. Dr _____, can you please tell me a bit about yourself, your area of practice and/or research interests?
2. What is your professional connection to rTMS? (in other words, do you conduct research in this area, do you facilitate rTMS in clinic, or a combination of both?)
3. Compared to your peers (e.g. other psychiatrists) how would you describe your level of experience with rTMS? For example, would you consider yourself an expert, more experienced, about the same experience, or less experienced?
4. For which conditions do you use rTMS as a treatment?

Experience with rTMS as treatment for TRD

5. When it comes to TRD, what is the general treatment pathway?
    - Is this the current standard of care (treatment pathway) in BC? *[If they follow a different protocol, what is it, and why?]*
6. In your experience, which clinical practice guidelines or best practice recommendations are typically used across the province?
7. For which types of patients are you most likely to recommend rTMS as a treatment?
    - How do these patients typically come into your care?

1. Approximately how many patients do you treat with rTMS each week? Month? (Year?)
2. When broaching the subject of rTMS with your patients, which other options do you typically discuss?
3. How do patients typically respond when you recommend rTMS?
    - What are some the concerns patients have about using rTMS?
        i. What do you tell patients who are worried about the treatment?

    - What are some of the barriers that prevent patients from using rTMS?

    i. Individual: Health conditions, philosophical objections, etc.
    ii. Structural: Costs, transportation, access inequity etc.

4. What alternatives do you offer patients when rTMS is not an option (either by choice or necessity)?
    - When given the choice, which option do your patients typically prefer?
    - Are there particular sub-groups of patients for which some options are better than others? If so, please explain.

Treatment Course

5. What is the general course of treatment? (for example, daily treatments for 3 weeks, etc.)?
6. Does the treatment course vary by patient? Can you tell me a bit more about this?
    - I understand that different clinics deliver different levels of TMS. What do you prefer in your practice, and why?
7. Once they start treatment, how often do patients continue with the full course, as recommended?
    - How often do patients drop out of treatment?
        i. When they do, do you have any sense as to the primary reasons?
8. What do your patients say to you about the physiological experience of undergoing rTMS?
    - For example, do they describe an experience of physical pain or other sensations? What do they say?
9. After treatment, what kind of follow up do you do?
    - Do you typically set up your patients with "maintenance" treatments? If so, what does that typically look like?
10. What do your patients say to you about the effectiveness of the treatment?
    - Overall, what is your sense of the impact of rTMS on patients' overall quality of life?
    - In your view, what is *the most important factor* for treatment success?
11. How often is it that treatment-resistant depression requires a secondary treatment alongside or in addition to rTMS?
    - Can you tell me about this?
12. What other factors might impact treatment outcomes?
13. Have you seen any complications emerge with rTMS? If so, please explain.

Coverage & Implementation

14. Across the province, how is rTMS typically paid for?
    - When rTMS is paid for out of pocket, what are the costs to patients?

- Do you know if any insurance companies cover rTMS, or have considered it?

15. BC's HTA of rTMS might mean the status quo, or other changes to how rTMS is paid for. In your view, what are the pros and cons of publicly providing rTMS?
16. How do you think healthcare coverage of rTMS could impact British Columbians?
    - For example: What is your sense of the number of British Columbians this could help?
17. Would you expect to see a lot of interest in this technology if it was to be offered within our public healthcare system?
18. What do you think needs to happen for rTMS to be implemented across BC?
    - For example, more machines purchased, training of healthcare professionals, establishment of clinical guidelines, etc.
    - What is the cost of a rTMS machine? What other resources are required for treatment (staff time, clinician time)?
19. If rTMS was to be offered publicly, what else do policymakers need to know?
20. If rTMS was to be offered publicly, what does the public need to know?

Closing Questions

1. Can you think of any other clinicians or health professionals we could speak to about this? We are hoping to connect with health professionals across all of BC's health authorities (e.g., Vancouver Island, Vancouver Coastal, Fraser Valley, Interior, the North).
2. What about patients – can you think of anyone who might be interested in sharing their experiences with us?
3. If we have questions or issues come up during our analysis, would it be okay to reach out to you by e-mail?
4. Is there anything else you'd like to add?

Thank you so much for your time.

16 Appendix D

CADTH Rapid Response Report

See attached PDF document.