EFFECTIVENESS OF REMINDERS VIA MESSAGING APPS IN IMPROVING CLINIC ATTENDANCE AND MEDICATION COMPLIANCE AMONG PATIENTS WITH DEPRESSION

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ABSTRACT

EFFECTIVENESS OF REMINDERS VIA MESSAGING APPS IN IMPROVING CLINIC ATTENDANCE AND MEDICATION COMPLIANCE AMONG PATIENTS WITH DEPRESSION

Background: Non-attendance at clinic appointments and medication non-compliance are both common issues within psychiatric settings, with forgetting being specified as one the most common reasons. This phenomenon may be worse for patients who are suffering from depression. Thus, the use of regular reminders in some format for such patients could be potentially very beneficial. With cognizance of the exponential growth of smartphone usage and social media awareness during the past decade, a messaging apps maybe a potentially efficient and cost-effective method of sending such reminders in a healthcare setting.

Objective: To determine the potential effectiveness of sending reminders via messaging apps to improve clinic attendance and medication compliance among patients with depression.

Methodology: This study used an open-label randomized controlled trial design. A total of 183 patients, all diagnosed with major depressive disorder (MDD) were recruited from two psychiatric clinics located in tertiary hospitals. All the participants were randomized into an intervention group and a control group, and followed-up over a period of two months. Participants in the intervention group received two types of reminders via their preferred apps: 1) Clinic appointment reminders which were sent a day before their allocated appointment date, and 2) Medication reminders which were sent weekly.

Results: The Intention-to-treat approach was used for the analysis of the 183 participants. At the close of trial period, the results presented a significant improvement of clinic attendance rates with the intervention group (76.8%) compared to the control group (56.4%) (P = 0.002). Similarly to medication compliance, the intervention group also presented a significantly higher BARS percentage (60.2%) in comparison to the control group (37.1%) (P < 0.001). In this study, the treatment given for the depression was generally effective in all participants as proven by the significant result of the MADRS score change in both groups with the P value of <0.001 respectively. Aside from that, it was found that the intervention group has a significantly higher mean score change (9.4, 95% CI [7.2, 11.6]) as compared with the control group (6.0, 95% CI [4.1, 7.9]) with a mean difference of 3.4 with 95% CI [0.4, 6.3] (P = 0.025). Hence, it may be inferred that there is a significant association between receiving reminders and depressive symptoms. As for reminder preferences, the majority of participants (53%) stated their concerns relate to forgetting. This response was in accordance with the result of reasons for defaulting on appointments, which showed 31% was due to forgetting. Unsurprisingly, WhatsApp was the most preferred messaging service amongst the participants by virtue of its high market penetration rate globally and in Malaysia.

Conclusion: Reminders via messaging apps were found to be effective in improving clinic attendance and medication compliance among patients with depression. Messaging apps, with high penetration and effectiveness are able to render useful service for reminder delivery within the healthcare setting.

Keywords: reminders; messaging apps; attendance; compliance; depression

ABSTRAK

KEBERKESANAN PERINGATAN MELALUI APLIKASI PEMESEJAN DALAM MENINGKATKAN KEHADIRAN KLINIK DAN PEMATUHAN UBAT DALAM KALANGAN PESAKIT DENGAN KEMURUNGAN

Latarbelakang: Ketidakhadiran pada temujanji klinik dan ketidakpatuhan dengan ubat adalah isu yang lazim dalam bidang psikiatri. Di antara sebabnya, lupa adalah salah satu sebab yang paling biasa. Keadaan ini boleh menjadi lebih teruk bagi pesakit yang mengalami kemurungan. Oleh itu, penggunaan peringatan secara berkala dalam format tertentu di golongan ini berpotensi sangat bermanfaat. Dengan pertumbuhan pesat kadar penggunaan telefon pintar dan kesedaran media sosial dalam satu dekad yang lalu, aplikasi pemesejan berpotensi sebagai kaedah yang efisien dan kos efektif untuk penghantaran peringatan dalam persekitaran perawatan klinikal.

Objektif: Untuk mengkaji keberkesanan peringatan melalui aplikasi pemesejan dalam meningkatkan kehadiran klinik dan kepatuhan ubat dalam kalangan pesakit yang mengalami kemurungan.

Kaedah kajian: Ini adalah kajian rawak terkawal dengan label terbuka. Sejumlah 183 pesakit yang didiagnosis dengan kemurungan direkrut dari dua klinik psikiatri dalam hospital berpakar (tertiary). Semua peserta diagihkan secara rawak ke dalam kumpulan intervensi dan kumpulan kawalan, diikuti dengan susulan selama dua bulan dijalankan. Mereka yang berada dalam kumpulan intervensi menerima dua jenis peringatan melalui aplikasi pilihan mereka: 1) Peringatan mengenai temujanji klinik yang dihantar sehari sebelum tarikh temujanji. 2) Peringatan mengenai ubat yang dihantar setiap minggu.

Keputusan: Pendekatan “intention-to-treat” telah digunakan untuk analisis 183 peserta.

Pada akhir tempoh kajian, keputusan menunjukkan peningkatan yang signifikan terhadap kadar kehadiran klinik dalam kumpulan intervensi (76.8%) berbanding dengan kumpulan kawalan (56.4%) (P= 0.002). Berkenaan dengan pematuhan ubat, kumpulan intervensi menunjukkan peratusan BARS yang lebih tinggi (60.2%) dengan signifikan berbanding dengan kumpulan kawalan (37.1%) ($P < 0.001$). Dalam kajian ini, rawatan untuk kemurungan didapati berkesan secara amnya pada semua peserta seperti yang dibuktikan oleh keputusan perubahan skor MADRS yang signifikan pada kedua-dua kumpulan dengan nilai P masing-masing <0.001. Di samping itu, didapati bahawa kumpulan intervensi mempunyai min perubahan skor yang lebih tinggi dengan signifikan (9.4, 95% CI [7.2, 11.6]) berbanding dengan kumpulan kawalan (6.0, 95% CI [4.1, 7.9]) dengan perbezaan min 3.4 dan 95% CI [0.4, 6.3]. (P= 0.025). Oleh itu, boleh disimpulkan bahawa terdapat hubungan yang signifikan antara penerimaan peringatan dan gejala kemurungan. Berkenaan dengan soal selidik peringatan, majoriti peserta (53%) menyatakan keprihatinan mereka terhadap isu lupa. Respon ini adalah serasi dengan keputusan mengenai sebab untuk mungkir janji temu, yang menunjukkan 31% adalah kerana lupa. Tidak menghairankan, WhatsApp adalah aplikasi pemesejan yang paling digemari oleh para peserta bersesuaian dengan fakta bahawa kadar penembusan pasarannya tinggi di seluruh dunia dan di Malaysia.

Kesimpulan: Peringatan melalui aplikasi pemesejan didapati berkesan untuk meningkatkan kehadiran klinik dan pematuhan ubat-ubatan dalam kalangan pesakit yang mengalami kemurungan. Aplikasi pemesejan, dengan penembusan dan keberkesanannya yang tinggi telah membuktikan kegunaanya untuk penghantaran peringatan di persekitaran perawatan klinikal.

Kata kunci: peringatan; aplikasi pemesejan; kehadiran; pematuhan ubat; kemurungan

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST ABBREVIATION

Abbreviation	Full Text
BARS	Brief Adherence Rating Scale
CI	Confidence Interval
DSM-5	Diagnostic and Statistical Manual of Mental disorders, 5th Edition
HM	Hospital Melaka
IQR	Interquartile Range
MADRS	Montgomery-Åsberg Depression Rating Scale
MCO	Movement Control Order
MDD	Major Depressive Disorder
SD	Standard Deviation
SMS	Short Message Service
TM	Text Message
UMMC	University Malaya Medical Centre

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

Depression is a common and substantial mental health problem within communities worldwide. A recent meta-analysis study estimated the worldwide prevalence of depression as 12.9%. Further, comparing among the continents, Asia ranked 2nd with a reported prevalence of 16.7%. (Lim et al., 2018). Due to this high prevalence, depression has become the leading cause of disability and overall global burden of disease worldwide.

With the advancement of current medical sciences in the past few decades, more evidences have shown that depression is a treatable disease by pharmacological and psychological therapy. Hence, early diagnosis, early treatment initiation, regular follow-ups and compliance to treatment are the key solutions to reduce the number of people suffering with depression in the community.

As we all know, one of the major challenges in the healthcare services is non-attendance at clinic appointments. Non-attendance not only leads to adverse health outcomes, but also increases healthcare costs. This situation exists in every medical specialty, but it is especially true in psychiatry services. In the psychiatry setting, non-attendance is one of the good predictors of poor outcome, leading to higher risk of relapse and the need of longer treatment periods. Non-attendance could be attributed to multiple factors such as a lack of insight and perceived need for treatment, stigma by the patients themselves and others towards mentally unwell patients. Poor cognitive functioning amongst psychiatric patients is a common contributing factor to non-attendance at psychiatric clinics. Among all the reasons given for non-attendance, forgetting is listed as one of the most common in primary care. (Martin, Perfect, & Mantle, 2005) (Neal, Hussain-Gambles, Allgar, Lawlor, & Dempsey, 2005).

In the context of depression, where depressive thoughts are present, individuals with a depressed mood show as much as a 12% reduction in memory functioning in comparison to individuals without a depressed mood. A plausible mechanism to explain this is that working memory capacity shows deficits in the presence of depressive thoughts. (Hubbard et al., 2016). Furthermore, other features of depression could also possibly contribute to non-attendance. Among them, lack of motivation is a cardinal feature of depression that generally is attributed to a reward-related deficit that can also lead to non-attendance. Dehn et al. suggested that a motivation-enhancing factor could benefit depressed individuals by improving their memory. (Dehn, Driessen, & Beblo, 2020). In line with this research, reminders could act as a motivating factor for patients to attend their appointments for the sake of treatment. Furthermore, individuals with depression often show significant under-confidence. (Fu, Koutstaal, Poon, & Cleare, 2012). This may explained why people with depression tend to be over-pessimistic due to negative self-concepts, based on the negativity hypothesis. (Clark, Beck, & Alford, 1999) (Gilboa-Schechtman, Erhard-Weiss, & Jeczemien, 2002). Hence, they might lack confidence in many aspects of their lives due to their pessimistic thoughts, inclusive of self-recovery from illness. In light of these aforementioned points, reminders are potentially beneficial for depressed individuals, not only in relation to forgetting prevention, but also as a motivating factor and a form of encouragement to continue their treatment in the clinic.

To date, there are plenty of studies available relating to clinic appointment reminders in the form of telephone calls, letters and text messages (TM). Most of the studies have proven the efficacy of all forms of reminder with some disparity in terms of cost-effectiveness, staff time and width of penetration. However, there appears to be no published study relating to reminders via mobile phone messaging apps to examine its efficiency in improving clinic attendance. In the new era of telecommunication technology, most people own a smart phone. In Malaysia alone, there has been a sharp

rise of smartphone penetration rates, from 7.2% in 2016 to 75.9% in 2017, followed by a steady rise to 78.0% in 2018, as reported by the national survey. (*Hand Phone Users Survey 2017*) (*Hand Phone Users Survey 2018*). In cognizance of this high penetration of smartphones in the population, messaging apps is potentially the most efficient method of sending reminders.

Along with non-attendance at clinic appointments, non-compliance to medication is another major problem existing in the field of psychiatry. This is linked with the patient's poor prognosis and incremental differences of treatment cost. The rate of non-compliance among patients with psychotic disorders is varied according to different studies. It ranges widely from 11% and can run as high as 80%. (Corrigan, Liberman, & Engel, 1990) (Breen & Thornhill, 1998). In the treatment of depression, the findings from different studies are also varied. Bulloch et al. reported the non-compliance rate at 45.9%, meanwhile Katon et al. and Lin et al. reported 60% and 72% respectively. (Bulloch & Patten, 2010) (Katon, von Korff, Lin, Bush, & Ormel, 1992) (Lin et al., 1995). Factors affecting compliance with psychotropic medications can be of many kinds. Forgetfulness is found to be one of the most significant factors among all which contributed to between a quarter to a half of the non-compliance cases. (Alshiekh, Ahmed, & Amasha, 2017) (Shrestha Manandhar et al., 2017). Among all the psychotropics, antidepressants are found to have the highest degree (74.5%) of reported forgetting as the reason of non-compliance. (Bulloch & Patten, 2010). In addition, the presence of depressive states such as reduced motivation to receive treatment, lack of confidence in recovery and mistrust in the medications prescribed could possibly result in non-compliance. This was suggested in the De las Cuevas et al. (2014) study which concluded that adherence to antidepressant usage was closely associated with the patient's attitudes and beliefs. (De las Cuevas, Peñate, & Sanz, 2014). Hence, sending an extra reminder regarding medication compliance in conjunction with the

appointment reminder could be a convenient way of tackling forgetfulness, while also motivating and encouraging depressive patients to adhere to their antidepressants.

It is noted that there are very few studies examining the impact of mobile phone TM for improving aspects of psychiatry care. According to a cross-sectional survey done by Donaldson et al. to assess the acceptability of using TM reminders in psychiatry clinic, only 53% of patients who owned a mobile phone and remembered their mobile numbers were agreeable to being contacted in this way. (Donaldson & Tayar, 2009). Sahm et al. reported higher rates of acceptability at approximately 60% among patients who had been prescribed with antidepressants and self-reported unintentional non-adherent. (Sahm, MacCurtain, Hayden, Roche, & Richards, 2009). Although TM reminders might be beneficial for those patients who are acceptable and consented to it. On the other hand, an online survey exploring community attitudes towards the use of mobile phones for mental health monitoring and management was undertaken and revealed that 76% of respondents favoured using their mobile phone for such purposes if the service were free. (Proudfoot et al., 2010). Another finding in this Proudfoot et al. (2010) study presented respondents with current symptoms of depression, anxiety, or stress to be more interested in possible implementation of such a program as compared to those without current symptoms. Based on the above, this research posits that sending reminders via messaging apps to depressive patients might be both favourable and beneficial to their mental health status and future well-being.

CHAPTER 2: LITERATURE REVIEW

2.1 Relationship between Depression and Forgetfulness

Depression is a psychological disorder that can extensively affect a number of aspects of a human life, inclusive of one's emotions, physical well-being, thoughts (cognition) and behaviour. Amongst all of these aspects, the effect of depression and antidepressant use on cognition remains the most featured in recent clinical research over the last few decades. This reflects the importance of cognition for the treatment of depression in line with the concept of aiming towards functional recovery as the ultimate goal of the treatment for depression.

Memory is one of the major domains of cognition. The memory process involves three main domains: encoding, storage and retrieval. Any defect of any of these domains would result in a memory deficit – forgetfulness. Amongst the great volumes of research, Strömgren et al. (1977) showed that depression is a proven cause of memory impairment. (Strömgren, 1977). A number of studies, inclusive of Sternberg and Jarvik (1976), found that depressed patients showed marked impairment in short-term memory without an impairment on long-term memory. (Sternberg & Jarvik, 1976).

In light of the recent advancements of research methods and radiology technology, more studies have been undertaken to explore the effects of depression on memory. Significantly, depression is found to be associated with impairment on memory encoding. (Burt, Zembar, & Niederehe, 1995). Furthermore, the researchers related this encoding deficit to medial temporal dysfunction. (Bearden et al., 2006). In addition to the memory encoding, there has also found to be a proven association between depression and autobiographical memory. (Lemogne et al., 2006).

Autobiographical memory includes autobiographical events (episodic memory) and autobiographical facts (semantic memory). (Lemogne et al., 2006).

In line with the above evidences, other studies have concentrated on looking into the particular aspects of memory affected in depression. For example, Bearden et al. observed poorer verbal recall and recognition among the depressed individuals. (Bearden et al., 2006). Other researchers have proposed the viewpoint of a "defective executive inhibitory mechanism" associated with depression. Conttencin et al. concluded from their study that depressed people have difficulty in inhibiting irrelevant information, thereby overloading their working memory and resulting in their difficulty in retrieval of specific episodic memories. This was attributed to a deficit of the prefrontal function. (Cottencin et al., 2008). A similar concept was introduced by Groome and Sterkaj, who suggested retrieval-induced forgetting (RIF) was deficient in depressed individuals. (Groome & Sterkaj, 2010). The RIF phenomenon is the act of retrieving a memory that has been found to suppress the recall of related memories.

2.2 Methods to Improve Clinic Attendance

Efforts towards improving attendance at clinic appointments amongst depressive patients if effective would be very promising in reducing morbidity of the individuals and prevent wastage of healthcare resources. Since forgetting is one of the main reasons for non-attendance, strategies were designed to target at reminding the patients and thereby prevent them from forgetting. Many studies and reviews have been undertaken in the past few decades to examine the various methods of improving attendance, significantly by the means of telephone and letter reminders.

Shivack and Sullivan (1989) in their study proved that telephone prompts made one day prior to the appointment date dramatically increased the attendance rates

among the psychiatric patients from 41.2% to 73.9 %. However, the method was found to only be effective if the patient could be reached directly. (Shivack & Sullivan, 1989). Ritchie et al. also reported significant improvements of attendance rates for all outpatient appointments referred from the emergency departments when telephone call reminders were used. In this randomized controlled trial, telephone reminders were sent between one and three days after the patients' attendance at the emergency department and showed an incremental improvement from 54.4% to 70.7% of attendance at scheduled appointments. (Ritchie, Jenkins, & Cameron, 2000). Furthermore, numerous studies involving different settings and designs have given promising results. (Macharia, Leon, Rowe, Stephenson, & Haynes, 1992) (Henderson, 2008). Hochstadt et al. proposed and found that the optimal time to remind patients through phone calls is one day before in order to significantly reduce the rate of missed appointments. (Hochstadt & Trybula Jr, 1980). Despite the promising efficacy of telephone reminder in reducing non-attendance at clinic appointments, the impact is still dependent on being able to contact patients via the telephone. (Henderson, 2008). Hence, telephone reminders might not be feasible in secluded areas where landlines and telco connections are poor, or residents of poverty who cannot afford the basic telecommunication service.

Letter reminders is another well-studied method and its efficiency in improving clinic attendance is evidenced a number of studies. (Macharia et al., 1992) (Henderson, 2008). Among the most significant, three studies have compared the different types of modified "standard" reminder (which only provide information regarding when and where). Parrish and colleagues found that "warning" reminders and "reward" reminders were more effective at increasing attendance rates than "standard" reminders. (Parrish, Charlop, & Fenton, 1986). The Krishna et al. (2012) study was undertaken to test the efficacy of letter reminders in a psychiatry setting. The study concluded that reminder letters within a week before the appointment can improve attendance rates in

community mental health clinics. (with significant results of 72% of attendance rate in the experimental group versus 57% in the control group.) (Krishna & Amarjothi, 2012). Rajasuriya et al.'s study conducted in a psychiatry outpatient clinic setting found that both telephone and letter reminders are equally helpful in reducing non-attendance rates from 31.2% to 23.1% with a relative risk reduction of 26.2%. (Rajasuriya, de Silva, & Hanwella, 2018).

Apart from reminders via telephone calls and letters, there are other evidenced methods to reduce non-attendance. A meta-analysis done by Macharia et al. examined the various interventions that may be used to improve clinic attendance of all medical services in general and discovered other rarer, but effective methods. Reminders via a patient's physician, orientation statements (providing information about reason for appointment and clinic organization) and contracting with the patient (acquire formal agreement to attend future appointment) are a few of the other methods proven to be workable. (Macharia et al., 1992).

2.3 Methods to Improve Medication Compliance

Depression is a treatable disease, yet its treatment is always hindered by medication non-compliance. The ability to improve compliance issues would carry forwards providing a big impact on the treatment for depression. Multiple interventions of various approaches have been examined to look for the most effective methods of improving medication compliance among the depressive patients.

In line with the effort to tackle forgetfulness in taking medications, reminder-based interventions are deemed to be workable. Fenerty et al. has conducted a meta-analysis to compare daily medication adherence in a group receiving reminders compared with the controls. Interventions used in the studies comprised of reminders in

the form of phone calls, text messages, pagers, interactive voice response (IVR) systems, videotelephone calls, and programmed electronic audiovisual reminder devices. The results showed a statistically significant increase in medication adherence in the intervention groups compared with the controls. (Fenerty, West, Davis, Kaplan, & Feldman, 2012).

More specifically, a pilot study by Reidol and colleagues investigated the use of IVR systems for prescription refill and daily medication reminders among peoples with chronic disease. The IVR systems used in their study consisted of two novel features: personalized, medication-specific reminder messages and communication via voice recognition. The study results showed that the majority found IVR systems are acceptable, despite many individuals experiencing technical and performance issues. (Reidel, Tamblyn, Patel, & Huang, 2008). Thereby, IVR technology is a potential strategy to improve medications compliance in the future, once the technical and performance issues have been addressed. It is feasible for those who are receptive to this technology and especially useful for patients with memory difficulties or complex medication regimens.

Other methods which have shown promising efficacy results in enhancing medications are in the forms of psychological interventions and education programs which improve compliance. These are aimed at other factors of non-compliance rather than forgetfulness. In the Hayward (1995) study, Medication Self-Management (MSM) intervention, inspired by the concept of motivational interviewing was implemented among patients with non-organic psychosis. The study yielded changes in patient attitudes towards medication and insight into their illness, thus improving medication compliance. (Hayward, 1995). There are also a number of programs that that has been shown to improve compliance among patients with depression and schizophrenia. Such examples include the medication group program, the educational compliance

enhancement program and the enhanced-care program. (Guimón, 1995) (Åkerblad, Bengtsson, Ekselius, & von Knorring, 2003) (Wade & Häring, 2010). Peterson et al. summarized all the interventions of the mainly behavioural and educational types to improve medication compliance and concluded that all interventions increase compliance by 4-11%. Furthermore, no single strategy appeared to be best. (Peterson, Takiya, & Finley, 2003). Finally, pharmacist interventions inclusive of in-person counselling and education to promote medication compliance have also been evidenced to enhance antidepressant compliance among depressive outpatients in a meta-analysis. (Readdean, Heuer, & Parrott, 2018).

2.4 Use of Mobile Phone Text Message / Short Message Service Reminders

In the new era of telecommunication technology, mobile phone use is very popular and has penetrated across all age groups, incomes and cultures. In view of this, the utilization of text message (TM) or short message service (SMS) for sending reminders in the healthcare setting has gradually been gaining ground in the past two decades. Furthermore, some research has reported growing interest in TM since 2006, along with the positive attitude of the public towards it. (Berrouiguet, Baca-García, Brandt, Walter, & Courtet, 2016).

Currently, there are a number of studies and reviews exploring the effectiveness of TM reminders in improving clinic attendance and medication compliance. In three different systemic reviews and meta-analysis, it was concluded that SMS reminders provide a substantial improvement in the appointment attendance in healthcare setting in general. (Robotham, Satkunanathan, Reynolds, Stahl, & Wykes, 2016) (Boksmati, Butler-Henderson, Anderson, & Sahama, 2016) (Guy et al., 2012). Boksmati et al. further described that the efficacy of SMS reminder is not affected by either when the

reminder is sent, or of the frequency and content of reminders. (Boksmati et al., 2016) On the other hand, Robotham et al. deduced multiple notifications could be significantly more effective at improving attendance than was a single notification. According to the review done by Kannisto and colleagues, involving different patient groups mainly comprising of HIV/AIDS and diabetes, 77% of the studies reported improved outcomes. Among those, 40% reported increase of compliance to medication, 18% reported increase of appointment attendance, and 18% reported decreases in the non-attendance rate. (Kannisto, Koivunen, & Välimäki, 2014).

There are a number of other studies comparing TM reminders with other forms of reminders such as phone call, letter, electronic mail and open access rescheduling. Stubbs et al. found that all 3 reminders (TM, phone call and letter) improve attendance, but at varying costs, with TM being the most cost-effective reminder system. (Stubbs, Sanders, Jones, Geraci, & Stephenson, 2012). Another review by Gurol-Urganci reported that TM reminders are similar to telephone reminders in terms of their effect on clinic attendance rate, but significantly superior than postal reminders or no reminders. (Gurol-Urganci, de Jongh, Vodopivec-Jamsek, Atun, & Car, 2013).

In Malaysia, there have been two randomized controlled trials examining a similar topic in primary care settings. (Leong et al., 2006) (Liew et al., 2009). Both studies were designed as sending reminders 24 to 48 hours prior to appointment. Leong et al. revealed that the attendance rate of the TM reminder group was significantly higher compared with that of the control group with an 11% increment. (odds ratio 1.59, 95% confidence interval 1.17 to 2.17, P = 0.005). However, no significant difference was reported compared with the phone call reminders groups. In addition, the cost of the TM reminder is about a half of the cost of the phone call reminders, hence it is deemed to be more cost-effective. (Leong et al., 2006). Similar findings were reported by Liew et al. where both TM group and the phone reminder group were comparably

effective with non-attendance rates significantly lower than the control group. (Liew et al., 2009).

With regard to the use of TM reminders in the psychiatry setting, comparatively less studies are available. Most studies are reviewed in non-psychiatry settings and involve non-psychotropic medications. Despite that, those non-psychiatry related studies examining the feasibility and usefulness of using TM to improve clinic attendance and medication compliance did provide useful evidence that supports the premise for further research into the use of TM in psychiatry. (IO Agyapong, K Farren, & M McLoughlin, 2011). Nonetheless, a systemic review has already been carried out by Berrouiguet et al. with regard to the use of TM in wide range of mental health situations, notably schizophrenia, affective disorder, substance abuse and suicide prevention. Furthermore, four ways of TM usage has been identified: reminders (14%), information (17%), supportive messages (42%) and self-monitoring procedures (42%). The benefits of using TM have been shown to comprise of improving treatment adherence and symptom surveillance, increase in appointment attendance and also in management and service satisfaction. (Berrouiguet et al., 2016).

These studies have shown promising results regarding the effectiveness of TM reminders in a psychiatry setting. The Donaldson and Tayar (2009), a small sample sized study summarized that an SMS reminder is a potentially useful and cost-effective method of improving psychiatric outpatient clinic attendance rates. (Donaldson & Tayar, 2009). Sim et al. conducted a pilot study by sending reminders at two different times to two different groups: the first group received reminders 7 and 5 days prior to appointment, and the second group received reminders 7 and 3 days prior to appointment. A control group which received no reminder was also included in the study. The results showed that missed appointments reduced to 9% and 10 % in both interventions respectively, and the risk reduction rate for failed attendance was 25% and

28% respectively. (Sims et al., 2012). The study by Kunigiri et al. further proved the effectiveness of a TM reminder with the result of an increased attendance rate from 72% to 80% ($P < 0.002$). (Kunigiri, Gajebasia, & Sallah, 2014) More significant results were reported by the Branson et al.'s study involving a sampling from adolescent patients in a psychiatric clinic. The study concluded that TM reminders that were sent a day before appointment showed significantly higher rates of attendance (65%) in preference to the control group (49%). Furthermore, the same study found that not only are TM reminders more cost effective, but they are also a more appropriate strategy for engaging adolescents and received high patient satisfaction ratings. (Branson, Clemmey, & Mukherjee, 2013).

2.5 Mobile Applications as a Novel Approach in Mental Health Service

Along with the popularization of smartphones around the world, the use of mobile apps especially messaging apps has achieved its popularity and widespread use. In an effort to outreach mental health services to the majority of the population, the role of smartphone apps, especially messaging apps in the field of mobile health (mHealth) is worth exploring.

New apps include the readily downloadable, free version of a mobile reminder application named Dosecast. Dosecast features reliable notifications, flexible scheduling, customizable dose amounts inclusive of instructions, and most importantly privacy and security settings. Dosecast has proven to significantly improve medication adherence when it is used along with coaching sessions in outpatient psychiatric clinics. (Trujillo, 2015). Another newly invented mobile app, specially designed for depression is called Medlink. Medlink is a systemic digital intervention intended to address failure points and improve treatment of depression in primary care. It provided dose reminders,

information and surveys of symptoms and side effects. A pilot study done to evaluate the feasibility of Medlink demonstrated patients show significant decrease in depressive symptoms, but a randomized control trial is now needed for the further development of this novel mobile apps. (Corden et al., 2016).

Messaging apps provide a platform that enables instant messaging and are the most widely used with smartphone apps. The popular ones include WhatsApp, Facebook Messenger, WeChat, QQ Messenger, Telegram, Viber, Line and Snapchat. (Wikipedia contributors, 2020). In view of their wide usage across the world, including here in Malaysia, it may be considered that messaging apps can potentially be used as a platform for sending treatment reminders, replacing the conventional methods of reminders such as letter, telephone calls. Apart from TM reminders which has already evidenced to be effective in improving appointment attendance, we posit that messaging apps could be another effective method of sending reminders outreaching to the depressive patients.

CHAPTER 3: RATIONALE AND OBJECTIVES

3.1 Rationale

Depressed individuals' forgetfulness and depressive states such as amotivation, pessimism about treatment and recovery are among the most common contributing factors to their non-attendance at clinic appointments and non-compliance to medications. Reminders via messaging apps is hypothesized to potentially be effective in helping depressed patients not only in reminding, but also motivating and encouraging them to adhere to their clinic appointments and medications. To date, there appears to be no published study on the efficiency of reminders via messaging apps in improving clinic attendance and medication compliance among patients in a psychiatry setting. Hence, this study has been designed to examine this method of reminder delivery, and determine whether it could be of benefit to patients diagnosed with a major depressive disorder.

3.2 General Objectives

To determine the efficiency of reminders via messaging apps in improving clinic attendance and medication compliance among patients with depression.

3.3 Specific Objectives

3.3.1 Primary Objectives

1) To compare clinic attendance rate between an intervention group (receiving reminders) and a control group (not receiving reminders).

2) To compare medication compliance between the intervention group and the control group by BARS assessment.

3.3.2 Secondary Objectives

1) To compare the improvement of depressive symptoms by MADRS score changes after two-months' intervention between the intervention group and the control group.
2) To explore depressed patients' perceptions regarding their preferences in receiving reminders, their concerns regarding confidentiality, the preferred timing, the frequency and the method of reminder delivery.
3) To explore the reasons for defaulting of clinic appointments among depressed patients.

3.4 Hypothesis

There are three sets of hypotheses tested in this study:

1) H_0: There is no significant difference in clinic attendance rates between the intervention group and the control group.
2) H_1: There is a significant difference in the clinic attendance rates between the intervention group and the control group.

1) H_0: There is no significant difference in medication compliance between the intervention group and the control group.
2) H_1: There is a significant difference in medication compliance between the intervention group and the control group.

1) H_0: There is no significant difference in MADRS scores change from pre- to post-intervention between the intervention group and the control group.
2) H_1: There is a significant difference in MADRS scores change from pre- to post-intervention between the intervention group and the control group.

CHAPTER 4: METHODOLOGY

4.1 Study design

This study was an open-label randomized controlled trial. All participants recruited were allocated at random to either the intervention or the control group. Both the researcher and the participants knew the intervention the participants were receiving, either they received reminders or did not receive any reminder. These two groups of participants were then followed up over time in order to compare their outcomes.

4.2 Study Population, Period and Setting

The participants were patients who were newly diagnosed with major depressive disorder (MDD) as the main diagnosis by doctors working in a psychiatry department, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria. These patients were screened by the researcher such that, only those patients who fulfilled both the inclusion and exclusion criteria were deemed eligible as a participant.

The study period was between February and June 2020. The samples were collected during the days when new patients were received. This included all weekdays in University Malaya Medical Centre (UMMC) and every Tuesday in Hospital Melaka (HM). Each participant was followed-up for the two months' period commencing from the day of recruitment, before they were reassessed by the researcher.

The study was conducted in two psychiatric clinics of two different states in Malaysia, according to the researcher's convenience. The first setting was the Psychiatry Clinic in UMMC, a university-based hospital located in Lembah Pantai, Kuala Lumpur, Malaysia. It operates from Monday to Friday, accepting new and

follow-up patients daily. Till the day of writing, it receives up to maximum of twelve new patients per day and the appointments are usually fully occupied on most days. On average, there are about 150 to 200 follow-up and walk-in patients daily. The treating doctors consist of psychiatrists and trainee psychiatrists who are students of Master program in UM. There are ten consultation rooms within the clinic and the pharmacy is in the vicinity of the consultation rooms.

The second setting was a Psychiatry Clinic in HM. It is a public hospital located in the city of Melaka, Malaysia. It serves as a referral centre for patients in the state as well as the northern part of Johor and the Tampin district of Negeri Sembilan. It receives follow-up patients from Monday to Thursday and new patients only on Tuesday mornings. The number of new patients ranges from 5 to 20 each day and follow-up patients range from 150 to 200 daily on average. The treating doctors are psychiatrists, psychiatry trainees and medical officers. There are four private rooms and two sharing rooms for consultation, together with a methadone room just within the vicinity. The pharmacy is a few steps walking distance away from the clinic.

4.3 Sampling Method and Sample Size

The convenience sampling method was adopted during sample collection in this study. Any patient who attended the psychiatric clinic in either UMMC or HM for the first time within the study period, and was diagnosed with MDD as the major diagnosis was approached by the researcher on convenience basis.

The sample size for this study was calculated using the formula as below, taking $\alpha = 0.05$, $\beta = 0.2$ and the expected proportion from the study by Branson et al. (Branson et al., 2013)

$$n = \theta[\frac{\pi_t(1-\pi_t) + \pi_c(1-\pi_c)}{(\pi_t - \pi_c)^2}]$$

The result of the sample size calculated was 154. Accounting for an acceptable dropout rate of up to 20% as rule of thumb (Furlan, Pennick, Bombardier, & van Tulder, 2009), the study aimed to recruit 193 samples.

4.4 Selection Criteria

The inclusion criteria are:

1. 18 years old and above.
2. Capable of reading and understanding English or Bahasa Malaysia.
3. Diagnosed with major depressive disorder as the main diagnosis according to DSM-5.
4. Prescribed at least one antidepressant by their treating doctor.
5. Owns a smart phone.
6. Consented to partake the study.

The exclusion criteria are:

1. Diagnosed with severe medical condition which may possibly affects one's cognitive function and physical ability to travel to hospital independently.
2. Diagnosed with other major psychiatric disorder with psychotic symptoms and/or severe cognitive impairment.

4.5 Instruments

1. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)

DSM-5 is the 2013 update to the Diagnostic and Statistical Manual of Mental Disorders, the taxonomic and diagnostic tool for psychiatric diagnoses published by the American Psychiatric Association (APA). In this study, it was used as a standardized diagnostic

tool among the treating doctors to diagnose MDD among their patients. As such, the samples recruited in the study were all diagnosed with MDD under the unified standard.

2. Socio-Demographic Questionnaire

The simple questionnaire consisted of seven items: age, gender, race, marital status, occupation, education level and distance from home to hospital. This self- administered questionnaire was given to each of the participants during recruitment in order to collect all the relevant socio-demographic information for the statistic use in the study. (Refer to Appendix E)

3. Treatment Reminder Preference Questionnaire

The questionnaire was designed to assess the participants' perception regarding their agreement for receiving reminders, concern regarding confidentiality, preferred timing, frequency and method of reminder delivery. The questions consist of:

1) Would you like to receive reminder for your clinic appointment via messaging apps? (Yes/No)

Please state your reasons. _____

2) Would you be concerned about confidentiality issues by receiving a reminder via a messaging app? (Yes/No)

If the answer to question (1) is "Yes", please answer the questions below:

3) When is your preferred time and frequency of reminder?

4) What is your preferred method of reminder delivery?

This questionnaire was given out to each of the consenting participants during recruitment for self-reporting. The results of this questionnaire were then used as a secondary outcome of the study. (Refer to Appendix F)

4. Montgomery-Åsberg Depression Rating Scale (MADRS)

MADRS is a clinician-administered scale for the assessment of depression which is particularly sensitive to treatment effects. It includes 10 items which are rated on a 0 to 6 scale (0 = no abnormality, 6 = severe). The overall score ranges from 0 to 60. Usual cut-off points are: 0 to 6 – normal, 7 to 19 – mild depression, 20 to 34 – moderate depression and > 34 – severe depression. It has demonstrated high inter-rater reliability and good validity and its scores correlate well with scores on a standard rating scale for depression - Hamilton Rating Scale for Depression (HAM-D). (Montgomery & Asberg, 1979)

MADRS is copyrighted by Stuart Montgomery, M.D. However, permission has been granted by the author to reproduce the scale from the website for researchers to use in non-industry studies. In this study, MADRS was used twice, the first time for all participants during recruitment and the second time for those who attended clinical appointments at the end of two months' period, in order to compare their depressive symptom's severity over time. (Refer to Appendix G)

5. Brief Adherence Rating Scale (BARS)

BARS is a clinician-administered adherence assessment tool consisting of two sections:

i) 3 questions about the patient's knowledge of their own medication regimen and episodes of missed medication taking, as follows:

1. Number of prescribed doses of medication per day.
2. Number of days in the past month when the patient did not take the prescribed doses
3. Number of days in the past month when the patient took less than the prescribed dose.

ii) A visual analogue scale (VAS) used to assess the proportion of doses taken by the patient in the past month (0–100%). The visual analogue scale rating is the key measure of adherence provided by the BARS.

BARS demonstrates good sensitivity (73%) and specificity (74%) in identifying non-adherent outpatients.(Byerly, Nakonezny, & Rush, 2008) It is freely available in the public domain, allowing unrestricted use of this scale. BARS was used to assess medication compliance for participants who attended their clinic appointments at the end of two months' study period. (Refer to Appendix H)

4.6 Method of Data Collection

After obtaining the ethical approvals from both the ethics committees, sample recruitment was first commenced in the Psychiatry Clinic in UMMC, and followed by the HM in accordance with the researcher's convenience. Prior to that, the head of department and sister-in-charge of the psychiatric clinic from each setting were informed about the study in order to obtain their permission.

Initially, all the potential participants approached were screened by the researcher, only those who fulfilled the inclusion and exclusion criteria were invited to participate in the study. Subsequently, the researcher gave them a participant information sheet and explanation regarding the details of the study. Meanwhile, they were also informed that they were not obligated to participate in the study and even if they consented to enter the study, they could withdraw at any time during the study period. Confidentiality throughout the study procedure was assured to all the participants. Once the participants agreed to participate in the study, the informed consent was obtained.

After consenting for study, each participant was required to fill up the Socio-Demographic Questionnaire, the Treatment Reminder Preference Questionnaire to assess their preferences in receiving reminders, and address their concerns regarding confidentiality issues, preferred timings, frequency and method of reminder delivery.

On completion of the above, pre-intervention MADRS assessment was undertaken before they were randomized to one of the groups: the intervention or the control group.

Randomization was carried out using a block randomization design and random number method. Every eight participants recruited were grouped into a subgroup called the block. Then, participants within each block were randomly assigned to each group by using a computer random number generator. Those randomized to the intervention group would receive two types of reminder via their preferred messaging apps. WhatsApp, WeChat, Telegram and Line were the popular choices.

i) Medication compliance at one week after the last clinic appointment and one-weekly thereafter.

"Hi, (name)

This is a reminder to take your medications as prescribed by your doctor in (UMMC or HM) on (date).

This is just a reminder system, please do not reply.

If you have any query or issue regarding the medicines, please do not hesitate to contact our pharmacy at (contact number) or come forward to our walk-in clinic to consult the doctor. We are open from ____ to ____ (opening days), ____ to ____ (opening time), except public holiday."

ii) Clinic appointment at one day before appointment date.

"Hi, (name)

This is a reminder that you have a clinic appointment in our clinic at (UMMC or HM) on (date) at (time) with Dr____.

This is just a reminder system, please do not reply. If unable to attend please contact the appointment counter at (contact number) for reappointment."

The control group did not receive any reminders. During the two months' study period, the clinic attendance of each participants was tracked via the EMR (Electronic Medical Record) system in UMMC (or daily manual attendance records in HM). This

was then double confirmed with the staff on the appointment counter to eliminate any uncertainties.

For those in the intervention group, if found to have defaulted, they would be reminded once for reappointment as below:

"Hi, (name)

This is a gentle reminder from (UMMC or HM). We noted that you did not attend your clinic appointment on (date) with Dr____. If you need a new appointment, please contact the appointment counter at (contact number) for reappointment. You may also walk-in if having any emergency situation."

The control group would not receive any reminder if found defaulted.

At the end of the two months' study period, the participants who attended their clinic appointment were assessed with post-intervention MADRS and BARS. The MADRS was assessed by the same investigator for pre- and post-intervention to ensure the maximum consistency of the scoring result. The difference between pre-intervention and post-intervention MADRS scores of each participant were then calculated. For participants who were absent during their appointment date, they were contacted via phone and the reasons for their default enquired into.

Lastly, all traced attendance of each participant was gathered and formulated into attendance rate. The primary outcomes of the study are the clinic attendance rate and medication compliance (BARS percentage) of each group. The secondary outcomes are MADRS score change from pre- to post-intervention within the group and comparison of MADRS score change between two groups, perception regarding treatment reminder preference and reasons for defaulting clinic appointment among depressed patients.

As the study progressed, those participants who fulfilled any of the withdrawal criteria could be withdrawn from the study at any time. The withdrawal criteria are as below:

i. The participant voluntarily withdraws his or her consent to participate in the study due to any reason.

ii. The participant transfers to another hospital or clinic for continuation of the treatment, either by due to his or her own or treating doctor's decision.

iii. The participant has passed away during the two months' study period after being recruited.

For those who transferred out to other hospital or clinic, they were informed via telephone call or messages regarding the decision of the investigator to withdraw them form the study. All the participants who withdrew from the study were not replaced.

4.7 Data Analysis

The data collected was analysed using the Statistical Package for Social Science version 23 (SPSS version 23). The intention-to-treat approach was used such that all of participants who were recruited and randomly allocated to each group were included. Post-intervention MADRS scores and BARS (%) for participants who were withdrawn from study or defaulted clinic appointments at the two months' stage were imputed as the last observed value, as per last observation carried forward (LOCF) method.

Initially, the data was summarized using descriptive statistics. Then, the relationship between the study parameters was analysed using the appropriate inferential statistical tests. All the statistical tests are two-tailed with the alpha value of 0.05. Below are the study parameters that were analyzed:

i) Socio-demographic data

The data consisted of age, gender, race, marital status, occupation, education level and distance from home to hospital. The data was summarized in total and in each group by using descriptive statistics. The baseline differences between the two groups were

assessed using different tests based on the type of variable. For categorical variables such as gender, race, marital status, occupation, education level and travelling distance, the Chi-square test was used. For numerical variables such as age, the normality test was undertaken to assess whether the data was normally distributed in each group. If normally distributed, the data would be analysed using an independent t-test. Otherwise, the non-parametric test - Mann-Whitney test would be the alternative option.

ii) Treatment reminder preference data

The questions asked included their preferences in receiving reminders, their concerns regarding confidentiality, the preferred timings, and the frequency and the method of reminder delivery. Descriptive statistics were used to summarize all the variables of the participants' preference in receiving treatment reminders to look for the frequency (n) and relative frequency (% percentage) in each categorized option.

iii) Reason for default

The participants who defaulted their clinic appointments at the two months' stage were contacted via phone and the reasons for the default inquired. Only answers from those who responded were then included in the analysis. Descriptive statistics were used to summarize the data into frequency (n) and relative frequency (% percentage) for each of the reason category.

iv) MADRS score changes from pre- to post-intervention within the group and comparison of MADRS score changes between two groups

On the day of recruitment, each participant was assessed using MADRS. Two months later, those who attended their appointments were reassessed with MADRS by the same researcher. The MADRS was intended to measure the change of depressive symptoms pre- and post-intervention in each group, and subsequently compare the score changes between the intervention and the control group. During the analysis, the normality test assessed for pre- and post-intervention MADRS scores of each group. For a normal distribution, the data would be analyzed using a paired t-test. Since the sample size is

big (more than 30 in each group), for a skewed distribution the pair-t test would be still appropriate to use. Secondly, the normality test was assessed for MADRS score changes of each group. If distribution proved normal, then an independent t-test would be used to analyze the data. If the data is skewed, Levene's test would be used to examine the population variances between two groups. If the test result is not significant, an independent t-test would still be appropriate to use. Otherwise, the Mann-Whitney test would be opted for instead.

v) Clinic attendance rate

This was calculated as the number of appointments attended divided by the total number of appointments scheduled within the two-month study period. Appointments that were missed by the participant were coded as absent. Appointments that were cancelled by therapists or rescheduled by participant ahead of time were excluded from the analysis. The data of attendance rate of each group was then assessed for normality. If normally distributed, an independent t-test would be used to compare the data for differences. If not, the Mann-Whitney test would be applied.

vi) Medication compliance - Brief Adherence Rating Scale (BARS) percentage

At the end of the two-months' recruitment period, only those participants who had attended their clinic appointments were assessed with BARS as they were expected to have collected their medications prior to that. The data of BARS percentage of each group was then assessed for normality. If normally distributed, an independent t-test would be used to analyse the data. If not, Mann-Whitney test would be appropriate to use.

4.8 Ethical Consideration

Ethical approvals for the study were obtained from the Medical Research Ethics Committee of University Malaya Medical Centre (MREC ID No 20191127-8047) and from the Medical Research and Ethics Committee of the Ministry of Health Malaysia via the National Medical Research Registry (NMRR) (NMRR ID: NMRR-19-3466-52001). The approval letters from both of the committees may be found in Appendix A and B respectively.

The nature of the research was explained to the participants using a Participant Information Sheet (Appendix C). Participation in this study was voluntary. Those patients who were invited were not obligated to join the study and even though they had consented to enter the study they can withdraw at any time during the duration. An informed consent (Appendix D) was obtained from all participants. Participants were assured that their confidentiality would be strictly protected during the study procedures at all times.

All procedures performed in the studies involving human participants have been managed in accordance with the ethical principles outlined in the Declaration of Helsinki 1964, inclusive its later amendments or within comparable ethical standards. Malaysian Guideline for Good Clinical Practice has also been applied.

CHAPTER 5: RESULTS

During recruitment, a total of 193 potential participants were approached for eligibility screening. The outcome of the recruitment found that 7 of the participants did not fulfil the inclusion criteria. Among them, one patient could not read and understand English or Bahasa Malaysia, 2 patients did not own a smart phone, and 4 patients were not prescribed any antidepressant. Meanwhile, 3 patients declined to participate in the study. Therefore, after 10 participants were excluded, there were a total of 183 eligible and consented participants. All of the 183 participants were randomized into two groups: the intervention group and the control group. Based on the randomization result, 92 participants were assigned to the intervention group while the remaining 91 participants were assigned to the control group. During the two months' study duration, one participant from the intervention group and 2 participants were withdrawn from the study due to transfer to other institutions by their own decisions. In addition, one participant passed way during the study period due to a worsening of her medical illness. A total of 179 participants reached the study endpoint. A detailed disposition of the participants is depicted in Figure 5.1. All participants recruited from the beginning of the study were included for the statistical analysis in accordance with intention-to-treat approach.

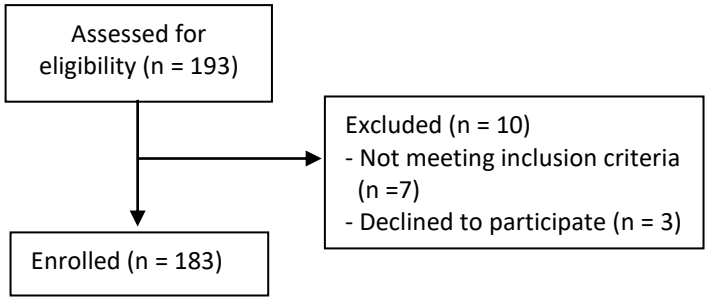

Figure 5.1, continued

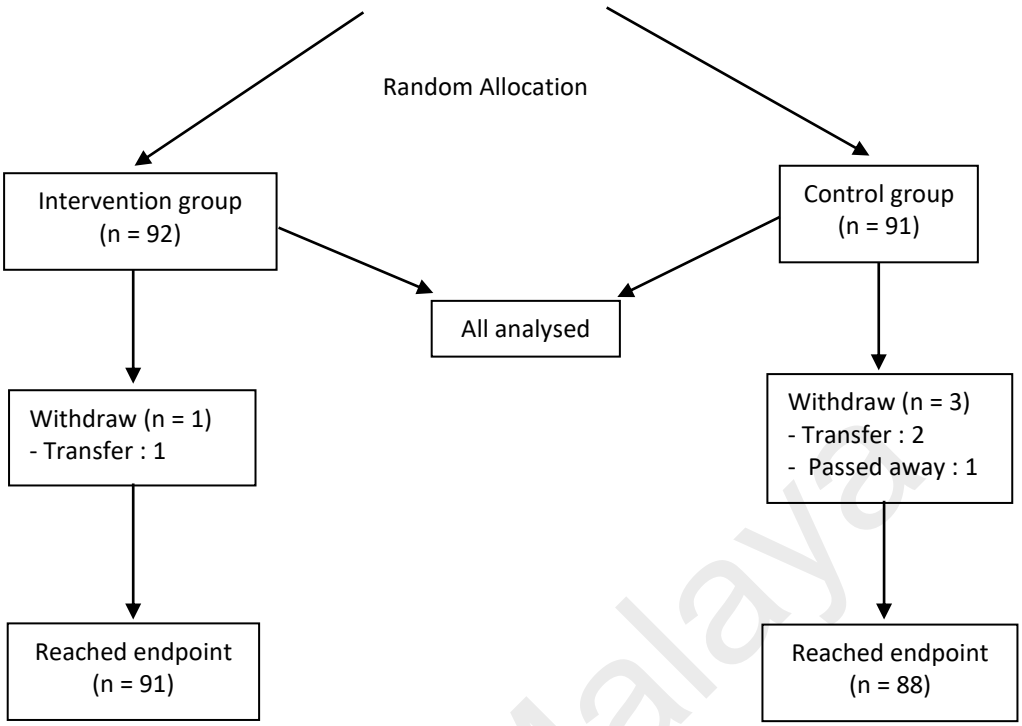

Figure 5.1 Disposition of Participants

5.1 Socio-demographics

Seven items of socio-demographic information were gathered from the participants. An overview of the results in total and separated by group is presented in Table 5.1. The overall results from the data analysis demonstrated no significant difference of all the variables between the two study groups.

The mean age of the overall participants in the study was 29.4 years with an SD of 11.71, while the median age is 25 with an IQR of 13. The intervention group and the control group have the same median of 25 respectively. Data analysis with Mann-Whitney testing showed that there was no significant difference of age between the two groups with the *P* value of 0.618.

In this study, the majority of the participants were female (66.7%, n = 122), double the amount of males (33.3%, n = 61). The similar distribution of gender was

seen in each separate group. The gender variable analyzed with Chi-square test demonstrated no significant difference between the two groups. (P = 0.464)

With regard to race, the proportion of each race within the total participants tally with Malaysia's population demographics profile. Malays occupied the top rank among all the races, comprising 68.9% (n = 126). Chinese ranked second, comprising 18% (n = 33), while Indians ranked third with proportion of 7.7% (n = 14). Other ethnicities only occupied 5.5% (n = 10) of the total participants. In each intervention and control group, the ranking of the races followed similar proportions. When analyzed with the Chi-square test, the results showed that there is no significant difference in terms of race between the two groups. (P = 0.271)

In terms of marital status, the majority of the participants were single, comprising 63.4% (n =116) of the total participants. Those who were married or in partnership occupied 32.2% (n = 59) and those who were divorced/separated or widowed occupied 2.7% (n = 5) and 1.6% (n = 3) respectively. The similar breakdown of marital status was observed in each group separately, with no significant difference when analyzed with Chi-square test. (P = 0.909)

The majority of the participants in the study were students and employed workers, comprising 39.9% (n = 73) and 36.1% (n = 66) respectively. Others were self-employed, unemployed, retired and homemakers, making up the minority of the participants. After randomization, student and employed workers still ranked first and second in each group, whereas the minorities have some discrepancy in their distribution. However, there were no significant difference found between the two groups when analysing with Chi-square test. (P = 0.205)

The education level, descriptive analysis revealed that most of the participants had higher education levels (66.7%, n = 122), followed by a secondary school level (23.0%, n = 42). Participants with a post-secondary level education occupied 8.7% (n = 16) and the last ranking was primary level (1.6%, n = 3). The same ranking was

observed when the data was analysed in separate groups. There was no significant difference of education level between the two study groups, as evidenced by the Chi-square test analysis with the *P* value of 0.779.

Lastly, the data on the travelling distance from house to the hospital was collected from the participants. The results showed that majority of the participants travelled 10 to 15km to the hospital comprising 32.8% (n = 60) of total participants. Numbers with respect to the intervention group was 33.7% (n = 31) and the control group was 31.9% (n = 29). All other participants' travelling distances were equally distributed among 3 categories: less than 5km, 5 to 10km and more than 20km. Chi-square test analysis of the travelling distance between the two study groups yielded no significant difference.

Table 5.1 Socio-Demographic Data

Variable		Total (n=183)		Intervention (n=92)		Control (n=91)		*P* value
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Age		29.4 (11.71)	25 (13)	30.5 (13.03)	25 (17)	28.3 (10.16)	25 (11)	0.618*
		n	%	n	%	n	%	
Gender:	*(M)*	61	33.3	33	35.9	28	30.8	0.464**
	(F)	122	66.7	59	64.1	63	69.2	
Race:	*(Malay)*	126	68.9	60	65.2	66	72.5	0.271**
	(Chinese)	33	18.0	17	18.5	16	17.6	
	(Indian)	14	7.7	7	7.6	7	7.7	
	(Others)	10	5.5	8	8.7	2	2.2	
Marital Status:	*(Single)*	116	63.4	58	63.0	58	63.7	0.909**
	(Married/ Partnership)	59	32.2	29	31.5	30	33.0	
	(Divorced/ Separated)	5	2.7	3	3.3	2	2.2	
	(Widowed)	3	1.6	2	2.2	1	1.1	
Occupation:	*(Employed)*	66	36.1	36	39.1	30	33.0	0.205**
	(Self-employed)	8	4.4	3	3.3	5	5.5	
	(Unemployed)	16	8.7	5	5.4	11	12.1	
	(Retired)	6	3.3	5	5.4	1	1.1	
	(Homemaker)	14	7.7	5	5.4	9	9.9	
	(Student)	73	39.9	38	41.3	35	38.5	
Education Level:	*(Primary)*	3	1.6	1	1.1	2	2.2	0.779**
	(Secondary)	42	23.0	19	20.7	23	25.3	
	(Post-secondary)	16	8.7	9	9.8	7	7.7	
	(Higher)	122	66.7	63	68.5	59	64.8	
Travel Distance:	*(<5km)*	41	22.4	21	22.8	20	22.0	0.354**
	(5-10km)	41	22.4	16	17.4	25	27.5	
	(10-15km)	60	32.8	31	33.7	29	31.9	
	(>20km)	41	22.4	24	26.1	17	18.7	

*Mann-Whitney test **Chi-square test

5.2 Perception Regarding Treatment Reminder Preference

In this study, 98.4% of the participants preferred to receive reminders for their clinic appointment and medication. Only 3 participants preferred not to receive any reminders, which comprised 1.6%. Among those who preferred to receive reminders, half (53%) were concerned with the issue of forgetting. Furthermore, 29.5% (n = 54) of these participants stated their reason of preferring reminders was to avoid forgetting, while 23.5% (n = 43) were reasoned out by their forgetfulness. Meanwhile, 16.4% (n = 30) stated convenience as their reason for preference to receive reminders. Other reasons given were health-conscious (n = 2), feelings of concern (n = 2) and other reasons such as "too many clinic appointments", "easy for preparation", for better communication" and "busy at work". A total of 24.6% (n = 45) of the participants did not state any reason for their preference of receiving a reminder. Amongst the 3 participants who preference was against receiving reminder, 2 mentioned "can remember without reminder", while the other participant perceived receiving reminders as a nuisance. With regards to concern about confidentiality, 43.7% (n = 80) answered "yes" while 56.3% (n = 80) answered "no".

Other questions explored from the questionnaire included the participant's preference over timing, frequency and method of reminder delivery. The descriptive analysis presented results as follows: The participants who preferred morning were 40.4% (n = 74); those who preferred evening were 27.3% (n = 50); the others advised afternoon, office hours and anytime, while 3 participants had no opinion. For the frequency of appointment reminder, the 5 most mentioned answers were one day before (20.8%, n = 38), 2 days before (19.7%, n = 36), 3 days before (15.8%, n = 29), 1 week before (14.2%, n = 26) , one week and one day before (10.4%, n = 19), 2 days and one day before (3.3%, n = 6) respectively. However, 13.3% of the participants have other less common answers and 5 participants did not have any opinion on this question. Relating to frequency of medication reminder, most of the participants (34.4%, n = 63%)

thought it unnecessary and 32.2% (n = 59) preferred a weekly prompt (32.2%, n = 59). Other answers were daily (10.9%, n = 20), twice per week (7.7%, n = 14), monthly (5.5%, n = 10), 2-weekly (2.2%, n = 4), once between appointment (4.9%, n = 9). Finally, 4 participants did not give their opinion. With respect to mode of message delivery, 87.4% (n = 160) preferred to receive reminder via WhatsApp. Other choices available were rarely requested. Table 5.2 gave an overview of the result as described above.

Table 5.2 Perception Regarding Treatment Reminder Preference

Variable	Option	n	%
Agreement	Yes	180	98.4
	No	3	1.6
Reason	Forgetful	43	23.5
	Avoid forgetting	54	29.5
	Convenience	30	16.4
	Health-conscious	2	1.1
	Feeling of concern	2	1.1
	Others	4	2.2
	No reason	45	24.6
	Reason of disagreement	3	1.6
Concern of confidentiality	Yes	80	43.7
	No	103	56.3
Timing of reminder delivery	Morning	74	40.4
	Afternoon	31	16.9
	Evening	50	27.3
	Office hour	5	2.7
	Anytime	20	10.9
	No opinion	3	1.6
Frequency of appointment reminder	1 day before	38	20.8
	2 days before	36	19.7
	3 days before	29	15.8
	1 week before	26	14.2
	1 week and 1 day before	19	10.4
	2 days and 1 day before	6	3.3
	Others	24	13.3
	No opinion	5	2.7
Frequency of medication reminder	Monthly	10	5.5
	2-weekly	4	2.2
	Weekly	59	32.2
	Twice per week	14	7.7
	Daily	20	10.9
	Once in between appointment	9	4.9
	Unnecessary	63	34.4
	No opinion	4	2.2

Table 5.2, continued

Method of reminder delivery	WhatsApp	160	87.4
	Telegram	13	7.1
	WeChat	1	0.5
	WhatsApp or Telegram	5	2.7
	WhatsApp or WeChat	1	0.5
	Disagree	3	1.6

5.3 Reason for Default

A total of 68 participants from both groups defaulted their clinic appointments within the two-months' period. A total of 58 participants responded to the question regarding the reason of their default, but 10 participants were uncontactable. The 58 participants who responded has their answers included for analysis. Forgetting the appointment was stated as the most common reason comprising with 31% (n = 18). The MCO (Movement Control Order)-related issue was second ranked with 20.7% (n = 12) by the participants whose appointment date fell within MCO period when travel restrictions were in place. Other reasons stated were personal issues (13.8%, n = 8), busy (12.1%, n = 7), feeling better (10.3%, n = 6), unsatisfied with the service (5.2%, n = 3) and physically unfit (5.2%, n = 3). One respondent was admitted to the ward for worsening depressive symptoms with a suicide attempt. An overview of the reasons for default is depicted in Table 5.3.

Table 5.3 Reasons for Default

Reason	n	%
Forget	18	31.0
Busy	7	12.1
Feeling better	6	10.3
Personal issue	8	13.8
Unsatisfied with service	3	5.2
Physically unfit	3	5.2
Admitted for relapse	1	1.7
MCO-related issues	12	20.7
Total responder	58	100

5.4 Improvement of Depressive Symptoms – MADRS Score

5.4.1 MADRS score change from pre- to post-intervention within the group

The pair t-test was used for analysis of the data pertaining to the respective groups. The intervention group reported a mean score change of 9.4 with 95% CI [7.2, 11.6]. This demonstrated that the MADRS score has increased significantly after treatment ($P < 0.001$). The control group's mean of score change was reported as 6.0 with 95% CI [4.1, 7.9]. The result of the pair t-tests was similar to that of the intervention group with a P value of < 0.001. In general, treatment for depression has resulted in significant improvements of the depressive symptoms in all the participants no matter whether they received reminders or not. The result of this is shown in Table 5.4.1.

Table 5.4.1 MADRS score change from pre- to post-intervention within the group

Variable	Intervention (n=92)					Control (n=91)			
MADRS score	Pre-I	Post-I	Mean of score change (95% CI)	*P* value		Pre-I	Post-I	Mean of score change (95% CI)	*P* value
Mean	32.7	23.3	9.4(7.2,11.6)	<0.001*	Mean	32.6	26.5	6.0 (4.1, 7.9)	<0.001*
SD	10.10	12.43			SD	9.53	12.14		

*Pair t-test Pre-I : Pre-intervention Post-I : Post-intervention

5.4.2 Comparison of MADRS score changes between two groups

Independent t-tests were used for analysis of the data. The mean difference of the MADRS score change between the two groups was reported as 3.4 with 95% CI [0.4, 6.3]. The analysis results demonstrated that the mean MADRS score change between the two groups was significantly different ($P = 0.025$). Therefore, there was a significant association between receiving reminders and depressive symptoms. The result is concluded in Table 5.4.2.

Table 5.4.2 Comparison of MADRS score changes between two groups

MADRS score change	Intervention (n=92)	Control (n=91)	Mean difference (95% CI)	t statistic (df)	Difference (*P* value)
Mean (SD)	9.4 (10.82)	6.0 (9.14)	3.4 (0.4, 6.3)	2.27 (181)	0.025*

*Independent t-test

5.5 Clinic Attendance Rate

The data of attendance rate was analyzed using a Mann-Whitney test. It showed that there was a significant difference of clinic attendance rates between the intervention and the control groups (P = 0.002). In other words, the use of reminders had a significant effect on the improvement of clinic attendance rate. The result is presented in Table 5.5.

5.6 Medication Compliance – BARS Percentage

The mean difference of the BARS percentage between the two study groups was reported as 23.1% with 95% CI [0.4, 35.8]. The result from the independent t-test analysis demonstrated that the mean BARS percentage between the two groups was significantly different (P < 0.001). It can be inferred that the reminders produced a significant effect on the improvement of medication compliance. The result is presented in Table 5.5.

Table 5.5 Attendance Rate and BARS Percentage

Variable	Intervention (n= 92)		Control (n=91)				Difference (P value)
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)			
Attendance Rate (%)	76.8 (35.31)	100 (50)	56.4 (44.51)	67 (100)	Z statistic -3.161		0.002*
BARS (%)	60.2 (43.05)	-	37.1 (43.97)	-	Mean difference (95% CI)	t statis-tic (df)	<0.001**
					23.1 (0.4, 35.8)	3.59 (181)	

*Mann-Whitney test ** Independent t-test

CHAPTER 6: DISCUSSION

6.1 Summary of Main Findings

The results of this study demonstrate that for this population reminders via messaging apps show a statistically significant improvement in clinic attendance and medication compliance among patients diagnosed with major depressive disorder. The study also reveals that for this population there was a significant association between treatment reminders and improvement of depressive symptoms, although the association factor was not explored.

The postulation that forgetting is one of the most common reasons for non-attendance of appointments among the depressed patients, based on the proven facts about the memory impairment in depression, was substantiated by the study's result. Among those who defaulted their clinic appointments, 31% of all the responders stated forgetting as their reason. This finding is in line with the Neal et al. study conducted in a primary care setting which reported over 40% of patients who missed their appointment cited "forgot" as their reason. (Neal et al., 2005). The idea of implementing reminder systems in the psychiatric clinic was welcomed by most of the participants, with 98.4% preferring to receive reminders. The reasons provided were mostly concerned with forgetting their appointments (53%) where 23.5% stated that they are forgetful and 29.5% stating that they need reminders to avoid forgetting.

Out of the 193 patients who were approached by the investigator, 183 participants were recruited. The recruitment and data collection process were very much hampered by the MCO which was implemented on 18th March 2020 in response to the COVID-19 pandemic leading to the number of sample recruitment being limited by the poor attendance of new patients seeking for consultation. The poor attendance was

possibly due to the travel restriction and the fear of going to the hospital. As a consequence, the recruitment process was slowed down in HM as it directly coincided with the MCO period. Of the 10 patients who were excluded from the study, only 2 did not own a smart phone (one of the inclusion criteria). This implies that the smart phone ownership rate among all the potential participants in this study is almost 99%, far higher than the reported smartphone penetration rate of 78% in 2018 (*Hand Phone Users Survey 2018*). It's ownership rate may be explained by the urban setting of the study where the people may potentially have a higher spending power. Only 3 patients refused to participate in the study when approached. This may reflect the acceptance of patients towards the idea of receiving reminders via messaging apps is good. The randomization process has categorized the participants equally between the two groups with intervention at n = 92 and the control group at n = 91. During the research period, 3 participants withdrawn from the study due to transfer to other institutions by their own decision and one participant passed away due to the unexpected worsening of her medical illness. Otherwise, none of the participant withdrew from the study upon their own request. Unsurprisingly, there were no direct or obvious adverse effects as a result of receiving reminders, unlike other interventional studies in which certain medication or invasive procedure are applied. As such, a total of 179 participants reached the study endpoint after the two months' period. There were 4 dropouts in the study. All 183 of the participants who were recruited and randomized were included for the data analysis in accordance with intention-to-treat approach. This is to ensure there is an unbiased comparison between the two study groups.

There was no significant difference in terms of baseline variables including age, gender, race, marital status, occupation, education level and travelling distance between the two groups. However, the sample of the study consisted of mostly young adults (mean 29.4 years) and females (66.7%). Since young adults often struggle to some

degree during the sensitive period of transition from adolescence to adulthood, this may explain the trend of higher rates of depression among younger adult. The gender disparity reflected the higher prevalence of depression in women in the general population. In 2010, the global annual prevalence of depression reported 5.5% in females and 3.2% in males respectively, representing a 1.7-fold higher incidence in women (Albert, 2015). A local review by Ng also concluded that in Malaysia, depression is more prevalent in women (Ng, 2014). In terms of race distribution, the ratio of each race in the sample resembled the general population in Malaysia with majority of Malay, followed by Chinese, Indian and other races. The majority of the participants in the study sample were single (63.4%), students (39.9%) or employed (36.1%), and having higher education level (66.7%). The similar trend of these variables was observed in both study groups after randomization. The travelling distance was a possible factor affecting the clinic attendance among the participants, and so was included as a baseline variable to be assessed. This was to ensure that travelling distance not being one of the confounders affecting the outcome of attendance rate. The result of analysis showed that there was no significant difference of travelling distance between the groups.

Due to the impact of MCO, the patient's attendance was tremendously reduced. For those in the intervention group who responded to the interview via phone call, most of them stated that they could not attend the appointment due to the interstate travel restriction, while a few stated that they were worried or fearful to go to hospital. Some were discouraged from going to hospital by their family members due to the same worries. The outcome was that the attendance of both the intervention and the control group was generally low during the MCO period, regardless of whether they received reminders or not. Notwithstanding that, the outcome of the study revealed that clinic attendance rate in the intervention group was significantly higher than the control group

(P = 0.002). This result implies that the use of reminders is effective in improving attendance rate among depressed patients. The finding of 20% increment of attendance rate in the intervention group compared with that of the control group in this study is apparently higher than the previous studies designed with sending TM reminders among patients of general psychiatry condition. Kunigiri et al. found 8% increment of attendance rate among adult patients while Branson et al. reported 16% increment among adolescents. (Kunigiri, Gajebasia, & Sallah, 2014) (Branson et al., 2013). However, the difference is that this study focused solely on depressed patients whereas the previous studies examined all patients with general psychiatric conditions. Furthermore, reminders were also proven to be effective in improving medication compliance among the depressive patients. This is concluded from the findings that the mean of BARS percentage in the intervention group (60.2%) was significantly higher compared with the control group (37.1%) with the *P* value of < 0.001. Apart from investigating the direct effect of reminders on clinic attendance and medication compliance, its indirect effect on the depressive symptoms was also examined in this study. First of all, the MADRS score change is each group was found to be significant, with the mean score change of 9.4 in the intervention group and 6.0 in the control group, both with the P value of < 0.001. These results suggest that treatment for depression with any antidepressant could result in a significant improvement of depressive symptoms in general, which is encouraging news for both the psychiatrists and patients. This study has also shown that reminders were significantly associated with the MADRS score improvement with a mean difference of 3.4 (95% CI 0.4, 6.3), and *P* value of 0.025. Although the associated factor was not investigated in this study, we hypothesize that it could be due to the combination of improvement of clinic attendance and medication compliance in the intervention group that led to the symptom's improvement. The exact associated factors could be further investigated in future research.

The other outcome from the study related to the patients' perception regarding treatment reminder preferences. This was deemed worthwhile to examine so that a reminder system which suits the majority interests could be designed in the future, in order to achieve the maximum effect in the clinic setting. As mentioned earlier, the idea of treatment reminders was well accepted by majority of the participants with more than half relating their concerns to forgetting. The response has proven further that memory could be an obvious problem among the depressive patients and reminders could be of paramount importance to help this group of patients. With regards to concern of privacy and confidentiality by receiving reminders, the majority (56.3%) of the participants responded "no" while 43.7% of them raised their concerns about the issue laid on the reminder system. The response reflected that privacy and confidentiality issue in the context of reminder system was not too alarming. However, there were still a significant number of patients who raised their concerns. Hence, it implies that efforts should be made while implementing any reminder system to address these concerns and improve the patient's trust towards the system. This may be done by ensuring that the content of the reminder message does not carry information such as the clinic name, medications or any other clinical information that could reveal the patient's clinical condition. Moreover, the questionnaire on the same title also looked into the participants' preference in terms of timing, frequency and method of reminder delivery. The response showed that there were diverse responses regarding the time and frequency of reminders although there was higher preference towards the mornings one day before for the appointment and for weekly medication reminders. This could be used as reference for the future implementation of reminder systems. On the other hand, there was one third of the participants who stated that medication reminders are unnecessary. Among them, some mentioned that they could remember the medication by themselves as they were prescribed only a single antidepressant, while several of them disagreed with the way of sending medication reminders in this study. They

suggested that the medication reminder could work like an alarm system whereby the message would reach them whenever it's time to take medication. In terms of method of reminder delivery, the majority of the participants (87.4%) preferred WhatsApp. In concordance, Malaysia tops the list for WhatsApp's market penetration with a rate of 68% pertaining to the third quarter of 2017 (Clement, 2019). In terms of the use of messaging apps amongst Malaysians, WhatsApp is the most preferred messaging service, followed by FB messenger, WeChat, Skype and Line. (Kemp, 2018). By knowing the preference of messaging apps of the majority, WhatsApp could be considered to be used as a platform to implement reminder system in the future. Lastly, by examining the reasons for defaulting on clinic appointments, some important information was revealed. The postulation of forgetting as the major factor of default among depressive patients was substantiated by majority (31%) of the those who responded by stating "forget" as their reason. In this study, as second half of the study period coincided with MCO, 20.7% of the responded defaulters stated MCO-related issues as their reason. This unprecedented implementation due to the COVID-19 pandemic has affected the study result to some degree. The other common reason was personal issues which was stated by 13.8% of the trial population. The personal issues were mostly unexplained, which could be due to the postulated depressive states such as amotivation and pessimism about treatment and recovery. Meanwhile, it was found that 10.3% of the participants defaulted when they felt better. It implied that the overall understanding about depression and its symptoms may be low within some of the patients. Therefore, psychoeducation to enhance patient's understanding about the illness and its treatment is important from the beginning of the treatment process.

6.2 Limitation and Strength

6.2.1 Limitation

There were a number of limitations recognized in this study. First, the reminder was sent out manually by one of the researchers and was not being counterchecked, therefore the accuracy of reminders delivery was unable to be evaluated and not warranted in this study. Secondly, despite participants being informed that the reminders sent would be a reminder system and no reply was required. However, the replies were unpreventable with several participants replying, mostly expressed their thanks. A few of participants asked questions in the apps. However, they did not receive any answer in this study. This phenomenon implied that some patients needed a platform to communication with the medical staffs. Since the messaging reminder in this study did not require any confirmation receipt of the reminders, it is uncertain whether all participants in the intervention group received the text messages. Resulting from that, the factor of whether the reminders successfully delivered was not taken into account in this study. Furthermore, the instrument used to assess medication compliance – BARS was only validated for oral antipsychotic use. However, it was used for antidepressants in this study as it was deemed suitable for tallying with design of the study. Despite a significant association being found between reminders and MADRS score improvement, the association factor was not explored in this study. Lastly, the study coincided with MCO. Therefore, the study result especially in relation to attendance was directly and obviously affected. The MCO has unavoidably became a confounder in this study.

6.2.2 Strength

Nevertheless, the study has a number of strengths. Since it involved two different types of setting, a university hospital and a government hospital, the sample better represents the population treating with depression in a psychiatric setting. The

preference regarding the type of messaging apps of each participant wished for was taken into account when sending reminders in order to ensure that the reminders were able to reach its maximum penetration to the recipients. The content of the reminder messages was designed in a way that the participants' privacy and confidentiality were well-protected as information which could possibly reveal a person's clinical condition was avoided. This is important to develop a sense of security and trust towards the reminder system. Lastly, most of the pre- and post-intervention MADRS of each participant were assessed by the same investigator except for a few cases where the attendance of the researcher was not possible. In this way, inter-rater inconsistency was prevented.

CHAPTER 7: CONCLUSION AND RECOMMENDATION

7.1 Conclusion

Forgetting was a major cause of defaulting clinic appointment causing non-attendance among patients with major depressive disorder in this study. Reminders via messaging apps, the popular and widely used communication platform were effective to improve not only clinic attendance and medication compliance, but also depressive symptoms indirectly among this group of patients. It was well accepted by the majority of the patients due to the forgetting-related concerns. Use of messaging apps would appear to be a highly penetrative and effective way of sending reminders in an effort to improve clinic appointment and medication adherence in the healthcare system especially for the depressed patients who have a tendency to be forgetful, unmotivated and pessimistic about treatment and recovery.

7.2 Recommendation

Future research could be undertaken using a similar design working with other groups of patients with other psychiatric conditions. It is hypothesized that it might be beneficial for other groups of psychiatric patients who may also experience forgetfulness and amotivation. Future research should involve a larger sample and over more diverse setting in order to achieve a better generalization to the population. With regards to the design of the reminders, the finding from this study about the participants' preference on timing, frequency and choice of apps could serve as a reference for future study. WhatsApp is recommended to be the first option as a platform to deliver reminder in view of its high market penetration and well-acceptance in Malaysia. In addition, a program linking the computerized appointment systems with

a messaging apps could be devised so that reminder messages would be generated and sent off automatically in order to reduce manpower and mistakes due to human errors. Ideally, adding an extra function on the reminder system by creating a communication forum between the patients and the medical staffs could be considered to expand the benefits of the reminder system. Lastly, a post-intervention feedback should be gathered so that any problems arising could be recognized and revisions of the reminder system addressed accordingly.

In clinical practice, reminders are a necessary part of patient treatment for major depressive disorders in psychiatric clinics. Using messaging apps for this purpose should be considered and prioritized due its high penetration and proven effectiveness. Nevertheless, measures to safeguard patient's privacy and confidentiality must not be neglected and need to be carefully planned.

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