Research Article

Implementing Video Consultations in a Rural Psychiatric Outpatient Clinic: A Feasibility Study

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Introduction. Multiple efficacy studies have shown that treatment provided via video consultation (VC) can be equivalent to in-person (IP) consultation for people with psychiatric diagnoses. However, despite the great promise of VC, it has not been widely implemented in psychiatric outpatient services. This study investigated the feasibility aspects of VC in clinical practice and examined a range of factors associated with the implementation of this modality of treatment within psychiatric outpatient services. Methods. This study had a pragmatic design, where 40 consecutive referrals for people with anxiety, personality, or depressive disorders were given the choice to receive eight weekly treatment sessions via VC or IP modality within an outpatient psychiatric setting. Information on demand, acceptance, engagement, implementation, and potential negative effects for treatment conducted via VC were collected to help identify factors that may impact on the uptake of VC within the psychiatric outpatient service. Results. There was a high demand and acceptance for VC, with 44% (n = 15) of the patients choosing to receive eight weekly treatment sessions via VC, and acceptance was rated highly. Engagement with VC modality was good, with only a very small percentage (13%, n = 2) not completing treatment. A good level of working alliance was established and largely maintained throughout treatment for patients and case managers. There were differences in the utilization of VC compared to the IP modality, with the VC modality having a greater focus on supportive counseling and IP modality having a greater focus on psychotherapy. Overall, the duration of treatment conducted via VC was also slightly shorter than that of IP consultations. There were no negative effects registered for consultations via video. Conclusions. Findings suggest a high patient demand and acceptance for VC within psychiatric services, with good levels of engagement and alliance reported. Differences in focus and duration in VC compared to IP may reflect clinicians’ different attitudes and/or approaches to providing treatment, depending on whether it is VC or IP consultations.

1. Introduction

Video consultation (VC) can offer additional benefits compared to in-person (IP) treatment, such as reducing travel time and associated costs and improving access to psychiatric treatment for patients who are unable to attend psychiatric clinics IP [1–4]. The scientific evidence base for the delivery of psychiatric treatments via VC has grown rapidly in recent years and the use of VC has been accelerated due to the COVID-19 pandemic and subsequent restrictions placed on direct social interactions. The vast majority of randomized controlled trials (RCTs) comparing VC to IP consultations have been conducted in the U.S.A. for patients suffering from posttraumatic stress disorder (PTSD), general anxiety disorder (GAD), and major depressive disorder (MDD) [5–11]. These studies have mainly
assessed the efficacy of VC compared to IP consultation in terms of symptom reduction, patient satisfaction, and therapeutic alliance, usually finding equal efficacy between the two intervention modalities. A recently published RCT (2021) by Acierno and colleagues tested the efficacy of prolonged exposure therapy (PET) for PTSD symptom reduction in 136 military trauma survivors [6]. The study compared VC to IP consultation and revealed no difference in PTSD symptom reduction between the two delivery modalities. Watts and colleagues [11] examined the impact of VC on the therapeutic alliance for patients with GAD diagnosis [11]. The study randomized 115 patients for conventional psychotherapy and measured therapeutic working alliance during the study. The authors concluded that the alliance was higher in the VC group. Hungerbuehler and colleagues [7] conducted an RCT enrolling 107 patients with MDD to compare the efficacy of psychiatric consultation conducted via VC [7]. No significant differences between groups regarding mental health status, satisfaction with treatment, therapeutic relationship, treatment adherence, or medication compliance were found in the study.

Despite promising efficacy results [12–14], there has been a limited uptake and use of VCs within psychiatry, indicating that there are significant gaps in the existing scientific research [15, 16]. There are a range of issues that could impact negatively on the implementation of VC in clinical settings. First, whilst RCTs are the gold standard in efficacy testing, they do not necessarily reflect the conditions within clinical settings. Thus, there is a need for research to examine the implementation of VC within everyday practice in order to obtain a clear picture of factors that facilitate and hinder the uptake of VC. Second, technology (including VC) is rapidly evolving, and there is a need to continuously evaluate these new (or modified) healthcare technologies within real-world environments.

In addition to the lack of research examining the potential factors that can facilitate or hinder the implementation of VC in outpatient settings, there are several other concerns highlighted by patients and clinicians which may limit the uptake of VC into clinical practice. These concerns include data security, user confidentiality, i.e., preventing unauthorized persons’ participation in the VC, lack of training and education in the technology, and limited technical support for end-users (clinicians and patients) when facing technical problems [15, 17–21]. Furthermore, some clinicians have expressed concerns about the ability to deliver high treatment quality, including personalizing therapy and establishing a high therapeutic alliance through VC technology [22–24]. Thus, it is necessary to examine factors such as acceptance and engagement with treatment via VC for both patients and clinicians in psychiatric settings.

Despite a range of concerns with VC, the COVID-19 pandemic has accelerated the uptake and widespread of VC. This rapid uptake, potentially without the necessary planning and support could potentially harm the continued uptake and implementation of VC in the post-COVID-19 era, particularly if the concerns and factors that limit the widespread use of VC in clinical settings are not identified and addressed [25, 26].

Despite the growing evidence base for the efficacy of psychiatric interventions via VC modality [12–14], there is an acknowledgement that video consultation is often underutilized in clinical practice [27–29]. The delay in the transfer of efficacious interventions from research to clinical settings is a recognized problem [30]. Understanding factors that facilitate and hinder the implementation of interventions into clinical practice (implementation research) is an important issue in ensuring people’s access to the best evidence-based treatments. The objective of this study was to assess the feasibility of VC, by evaluating the demand, acceptability, engagement, implementation, and potential negative effects of treatment provided by VC technology within clinical practice.

2. Material and Methods

The Consolidated Standards of Reporting Trials (CONSORT) extension for feasibility studies is applied to report this feasibility study [31].

2.1. Design and Settings. The study had a pragmatic design where consecutive 40 referrals to a rural psychiatric outpatient clinic were able to choose between two primary modes of treatment delivery: VC or IP consultations. People referred to the clinic had a diagnosis of depression (F30), anxiety (F40), or personality disorder (F60) according to the International Classification of Diseases, 10th Revision (ICD-10). The IP group was included as a reference group to identify potential differences regarding implementation (focus and duration). The participants were recruited from a rural outpatient clinic in Region Zealand, Denmark, from April 2021 to November 2021. The mental health employee (case manager) in the clinic consisted of five psychiatric mental health nurses, two medical doctors, three psychiatrists, one social and health assistant, and one peer worker. The outpatient clinic provides treatment for patients with nonpsychotic mental health disorders and includes supportive counseling, psychoeducation, psychotherapy (individual or group therapy), and pharmacological treatment.

2.2. Participants. Participants were eligible to be included in the study if they were over 18 years of age, were psychiatric outpatients with a diagnosis of anxiety, depression, or personality disorder, and were fluent in Danish. Eligible patients were primarily restricted to new referrals. Exclusion criteria included a diagnosis of schizophrenia or bipolar disorder, or suffering from substance abuse. The participants provided informed consent before inclusion in the study. Recruitment started after obtaining institutional review board approval (REG-003-2021).

2.3. Interventions. Both groups were offered eight weekly case management sessions (i.e., individual treatment as usual) [32]. The case management included therapy (psychotherapy and psychoeducation), medication management, training in daily living skills (supportive), and direct intervention in crises.
Patients were offered the choice between primary delivery modalities, that is, either VC or IP consultations. The VCs were performed using a secured and encrypted line through the patient’s portal of the electronic health record (EHR) of the hospital/clinic. The EHR was accessed through a smartphone app or a web application. Patients in the VC group received an instruction manual on how to connect to and use the VC technology before the first consultation. Two clinical secretaries employed in the outpatient clinic assisted the case managers in scheduling the eight weekly VC sessions and assisted when technical obstacles occurred during the video sessions.

2.4. Measures. Information was collected from patients and clinicians concerning a range of factors relating to the feasibility of implementing VC within a clinical setting.

2.4.1. Demand. The demand for VC was evaluated by the percentage of participants who chose VC as a treatment modality and the number of participants who completed treatment.

2.4.2. Acceptability and Engagement. Participants’ acceptability with the delivered consultation modality was evaluated using the Client Satisfaction Questionnaire (CSQ-8). The CSQ-8 consists of 8 items and provides a general score ranging from 8 to 32. Higher scores indicate higher global satisfaction. The scale possesses a high internal consistency (coefficient alpha: 0.91) [33]. Acceptability was measured at baseline and posttreatment.

Engagement was measured for both patients and case managers using the client and therapist versions of the Working Alliance Inventory (WAI-C and WAI-T). The instrument consists of 12 items and provides a general score, ranging from 12 to 84. Higher scores indicate a higher therapeutic alliance (coefficient alpha: 0.93) [34]. Engagement was measured at baseline and posttreatment.

2.4.3. Implementation and Potential Negative Events. After each case management session (weekly basis, for eight weeks), the case manager completed an implementation and integration checklist. The checklist was based on recommendations for assessment and outcome measures for telemental health [35]. The checklist was used to explore the implementation characteristics of VC and consists of the following five items:

(a) The focus of the VC sessions (supportive, therapy, medication management, crisis/acute, “mixed” focus, and other focus)
(b) Duration of VC session (length of session)
(c) The VC sessions’ confidentiality (alone or with other persons during VC)
(d) Type of technology patients used for VC sessions (smartphone/tablet or personal computer/laptop).
(e) Patients’ physical location during VC session (home or outdoor)

The focus and duration of each session were also recorded for IP consultations. The occurrence of negative events for both the treatment groups was carefully monitored during the study period. This monitoring included registration of severe adverse events (attempts of self-harm and suicide and hospitalization) and unwanted events that could potentially be experienced negatively or distressingly by the patients (e.g., technical problems with VC) [36]. Symptom deterioration was monitored using the symptom checklist (abbreviated version) (SCL-10). The checklist consists of 10 items, and the total score ranges from 0 to 100 and was measured at baseline and posttreatment. A lower score indicates lower psychological distress (coefficient alpha: 0.88) [37].

2.5. Sample Size. Examination of patient referral flow for the outpatient clinic and designated time for patient recruitment and completion of treatment, indicated that a total sample size of \( N = 30 \) (15 in each treatment modality) was determined to be realistic without significantly impacting on the daily practices of the clinic. The sample size was guided by previously published feasibility studies that have examined VC within mental health services [38–40].

2.6. Analytical Methods. Descriptive statistics were used to examine the feasibility outcomes and included percentage values, means, and standard deviations. A paired samples t-test was applied to examine within-group changes in engagement and acceptability from baseline to posttreatment during the study period for the VC group. The basic assumption regarding the normal distribution of the data was checked with the Shapiro–Wilks normality test before we conducted the paired t-test. Analysis was conducted in R version 4.2.2.

3. Results

3.1. Baseline Characteristics and Demand. A total of 40 patients were approached to participate in the study and offered a choice between treatment via VC or IP. A total of 34 participants agreed to participate in the study (85% response), and 44% (\( n = 15 \)) chose to receive eight weekly scheduled VC as a primary modality. The VC group’s completion rate (completed preassessment and postassessment) was 86% (\( n = 13 \)). There were two participants (13%) who dropped out from the VC treatment modality, and three participants (16%) who dropped out from the IP treatment modality.

Table 1 contains a summary of participant characteristics. The majority of included participants within the VC group were diagnosed with personality disorders (53.3%) and anxiety disorders (40%), and they had a mean age of 29 years. Patients who selected the IP modality had a diagnosis of anxiety disorder (63%), depression (21%), and personality disorder (16%).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personality disorders</td>
<td>53.3%</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>40%</td>
</tr>
<tr>
<td>Depression</td>
<td>21%</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>16%</td>
</tr>
</tbody>
</table>

The majority of included participants within the VC group were diagnosed with personality disorders (53.3%) and anxiety disorders (40%), and they had a mean age of 29 years. Patients who selected the IP modality had a diagnosis of anxiety disorder (63%), depression (21%), and personality disorder (16%).
3. Acceptability and Engagement of Video Consultation. Table 2 shows the patient’s scores in satisfaction (acceptability) and working alliance (engagement) with treatment through video technology. The overall pre-post test did not reveal any significant decrease or increase in scores and hence there were high levels of acceptability and engagement with treatment conducted through VC. Whilst there was a slight decrease in working alliance for case managers, this decrease was insignificant.

As the focus of the study was on feasibility, it was not designed or powered to detect the between-group effects or efficacy of the two treatments. Visual inspection of changes from pretreatment to posttreatment indicated that both groups experienced a decrease in psychopathology. Independent t-tests comparing change scores between the IP and VC groups and analyses of covariance (ANCOVA) after adjusting for baseline test scores indicated no difference between groups (Supplementary 1). The between-group comparison should be interpreted with caution given the study’s limitations.

3.3. Implementation and Negative Events. Overall, 104 (n = 13) consultations were conducted for the VC group and 128 (n = 16) for the IP group. The case managers conducting treatment through video technology reported that 45% of sessions had a supportive focus compared to 19.8% of sessions in the IP consultations. For the IP consultations, case managers reported that 66.3% of sessions had the main focus on psychotherapy compared to 7.8% for the VC modality. Figure 1 shows the focus of the VC and IP groups over eight weekly administered case management sessions.

Regarding the duration of sessions, the majority of sessions for both IP and VC groups lasted between 30 and 60 minutes (65% and 68%, respectively). There were some clear differences between the two groups with the VC group reporting 25% of sessions lasting 15–30 minutes, compared to 5% for IP sessions. Conversely, case managers reported that 26% of IP sessions lasted over 60 minutes, compared to 2.5% of video sessions. Thus, there was a tendency for VC to be shorter in duration than IP treatment. Figure 2 shows the duration of the two groups’ eight weekly administered case management sessions.

The results for negative and adverse events did not reveal any severe events (self-harm, attempted suicide, or hospitalization) during the study period. Participants decreased significantly in levels of psychopathology as measured with SCL-10 (P < 0.001, Table 2). Participants' confidentiality (i.e., being alone during the VC) was achieved successfully in 96.3% of all conducted video sessions. Most of the conducted video sessions took place while the patients were at home (78.75%). During the study period, 3.9% of the consultations in the VC group were converted to telephone consultations due to a lack of audio/video transmission, and no other unwanted events were reported.

4. Discussion

The following study examined the feasibility of VC in a rural psychiatric outpatient clinic and investigated how VC was implemented and integrated into clinical practice. Participants were able to choose between 8 weekly scheduled treatment sessions via VC or IP.

4.1. Demand. First, a significant proportion of participants (44%) choose to receive treatment via VC.

This finding would support the idea that many patients are willing to use video as the primary modality to receive treatment for their mental health problems. Acknowledging the relatively small number of participants, it was interesting that a significant proportion of patients with personality disorders showed a preference for treatment via VC (53%) compared to IP (21%). Some studies have shown that certain patient groups (e.g., patients with avoidant personality traits) find treatment via VC as less confronting and more acceptable than face-to-face consultations [41].

As the study was conducted during the COVID-19 pandemic, there was a general increase in VC uptake in Danish psychiatric services and worldwide [25, 26]. The impact of the pandemic on psychiatric services within Denmark was limited compared to many other countries as there was no hard lockdown restricting movement or access to psychiatric services. The majority of service users could still receive IP services. The pandemic also allowed many clinicians to obtain practical experience on using VC technology. Whilst some clinicians may have been

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pretest (SD)</th>
<th>Posttest (SD)</th>
<th>Paired t-testa t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSQ-8 (acceptability)</td>
<td>23.42 (6.31)</td>
<td>25.07 (5.83)</td>
<td>−1.0968</td>
<td>0.2942</td>
</tr>
<tr>
<td>WAI-C (engagement)</td>
<td>62.29 (17.21)</td>
<td>67.84 (11.51)</td>
<td>−1.4433</td>
<td>0.1745</td>
</tr>
<tr>
<td>WAI-T (engagement)</td>
<td>65.64 (6.64)</td>
<td>60.53 (9.89)</td>
<td>2.1477</td>
<td>0.05286</td>
</tr>
<tr>
<td>SCL-10 (symptoms)</td>
<td>70.19 (14.41)</td>
<td>59.61 (18.22)</td>
<td>3.1014</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*aPaired t-tests were calculated for the completers (n = 13), and the degree of freedom (df) was 12. CSQ-8, Client Satisfaction Questionnaire; WAI-C, Working Alliance Inventory-client version; WAI-T, Working Alliance Inventory-therapist version; SCL-10, symptom checklist.

### Table 1: Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VC (n = 15)</th>
<th>IP (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean (SD))</td>
<td>29 (12.8)</td>
<td>34.3 (15.3)</td>
</tr>
<tr>
<td>Females (n (%))</td>
<td>10 (66.7)</td>
<td>10 (52.6)</td>
</tr>
<tr>
<td>Diagnosis (n (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>6 (40)</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>8 (53.3)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (6.7)</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>The number of meetings with the case manager before inclusion in the study (mean (SD))</td>
<td>1.7 (2)</td>
<td>2.4 (4.1)</td>
</tr>
</tbody>
</table>
pressed to use VC without sufficient time and opportunity to integrate the technology into their daily clinical settings, a large survey (n = 819) examining clinicians’ attitudes towards telepsychiatry revealed that 64% of respondents would still continue to use telepsychiatry in the post-COVID-19 era [25].

4.2. Acceptance and Engagement. There were good levels of acceptance and engagement for the treatment via VC. The slight increase in satisfaction (acceptance) and the therapeutic alliance (engagement) for patients during treatment may be explained by the fact that most participants had the opportunity to meet their case managers before inclusion in the study which may have helped to establish a good rapport from the start.

It was interesting to note that case managers reported a slight reduction in engagement (working alliance) during treatment. These findings are consistent with a number of studies suggesting that patients in general have a positive attitude towards the VC modality, compared to clinicians who can have a more skeptical view [15, 22]. A decrease in alliance by case managers could be one explanation for the finding of a greater focus on support rather than psychotherapy in the VC group. In addition, as the duration of sessions was shorter in the VC group, this may have also contributed to a lower therapeutic alliance. Given the nature of the study design, it is not possible to infer direction or causality in relation to session focus, duration, and levels of alliance but it is worthy of further investigation.

Traditionally, most of the advantages of utilizing VC as a modality for psychiatric treatment have focused on the advantages from the patient’s perspective. These potential advantages of VC are many and include reducing travel time, improving access to psychiatric treatment, increasing the flexibility of interventions provided, and reducing stigma [1–4]. It is possible that researchers need to focus more on the potential advantages for clinicians in adopting VC as a part of their clinical practice, particularly as clinicians have been called the “gatekeepers” in regard to patients’ access to technology [15]. Future studies should examine how VC can be made more attractive for clinicians. One suggestion could be the option for clinicians to conduct VC from their homes. To our knowledge, no studies have examined outcomes for VC for clinicians administrating therapy at home, compared to administrating therapy at the clinic. Another suggestion to facilitate the implementation of VC in clinical practice and improve the uptake could be designing specialized environments and rooms with high-tech video equipment, a feature often missing in clinical practice. These specialized telemedicine rooms could positively contribute to the clinicians’ sense of connectedness and therapeutic alliance with the patient during virtual consultations [42].

4.3. Implementation and Negative Events. The study results showed a clear difference in the focus and duration of consultations between the two modalities. Psychotherapy was reported more often in the IP group (66.3%) than in the VC group (7.8%). This finding is consistent with other studies that have shown that clinicians have concerns about administering therapy through VC [22–24]. There may be several reasons for this finding. First, clinicians may have many years of experience in treating patients through IP modality and may find it difficult and challenging to switch to a new treatment modality (i.e., VC). Second, the extra time required for clinicians to learn new technical systems, in a busy and stressful working
environment may be considered as not relevant or efficient use of their time. Finally, there is the body of research indicating that some clinicians are concerned about the ability to establish a good therapeutic alliance via VCs due to a perceived lack of closeness, connection, and “virtual in-person sense” with patients through the VC [15, 43, 44]. Telepresence, which refers to “the illusion of being there, in the therapy room with the other person” [45] should be investigated more closely, as it can impact the digital working alliance during psychotherapy [46] and potentially the successful implementation of VC in clinical practice. The therapeutic alliance is seen as one of the key predictors of good outcomes in psychotherapy [14, 15].

The majority of VC and IP consultations lasted between 30 and 60 minutes, although there was no clear overall trend that VCs were shorter in duration than IP consultations. One potential explanation for this difference could be that the focus in VC was often support rather than therapy and therefore it was possible to hold briefer sessions. Screen time fatigue could be another explanation for the shorter sessions observed in the VC modality [15]. It is also acknowledged that differences in the diagnostic composition of the VC and IP groups may have contributed to the differences in treatment duration. The VC group consisted of 40% with an anxiety diagnosis, 7% with depression diagnosis, and 53% with personality disorders whilst the IP group had a composition of 63% with anxiety, 16% with depression, and 21% with personality disorders.

It is worth noting that whilst this study provided an estimate of the session time between the two modalities it did not measure the time spent on administrative tasks, e.g., setup time and out-of-session contact such as e-mail, text, phone, and letters. Measuring time spent on administrative tasks is an important aspect of understanding the implementation of telemedicine interventions in clinical practice [35].

In addition, clinicians may have some concerns regarding maintaining patient confidentiality using video conferencing, which could contribute to clinicians’ reluctance to use VC as a modality for therapy [15, 19, 23]. In the current study, confidentiality did not appear to be an issue, where the majority of VCs were conducted with only the patient present. Furthermore, no negative events were reported, and a decrease in symptomology was observed for the treatment using VC, which aligns with published studies investigating VC use within mental health settings [10, 38, 40].

4.4. Limitations. The results from the feasibility study are promising but there are several methodological, clinical, and statistical limitations. First, the study had a pragmatic design, which reduced the confidence of the overall findings, compared to more rigorous, randomized, and controlled studies. As participants were able to choose treatment modality, the nonrandomized nature of the study, may have biased our findings, as participants may have had positive ideas about VC before starting treatment. Second, most results were based on self-report and the use of more objective measures (e.g., observed focus in sessions) would have strengthened the findings. Finally, the sample size was small and, the participants were clinically heterogeneous, which limits the generalizability of the findings. Other feasibility studies examining the implementation of VC within psychiatric settings have had similar sample sizes [38–40] and it is hoped that the results from our study could be used to inform the planning of larger RCT examining VC in a wide range of diagnoses and psychiatric settings.

5. Conclusion

This study investigated how VC was utilized in clinical practice and examined the feasibility of treatment provided via VC. Overall, there was a high patient demand, acceptance, and engagement for treatment through VC, indicating that this modality is a feasible option in clinical practice. It was observed that the user of the VC modality displayed a tendency towards a more supportive usage and slightly shorter duration compared to treatment via the IP modality. Case managers using the VC modality showed a slight decrease in the therapeutic alliance, although the level of the alliance was still considered good. Future studies should investigate how to support and encourage clinicians to utilize VC in clinical practice and how to increase the “telepresence” in order to increase VC uptake in psychiatric treatment settings.

Data Availability

The data used to support the findings of the study are available from the corresponding author upon request. Data from the study can be made available via Region Sjaelland following the Danish Data Protection Regulation.

Ethical Approval

This study was approved by the Region Zealand, Denmark Ethics Committee (EMN-2021-00019). Recruitment started after obtaining institutional review board approval (REG-003-2021).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

AS is the guarantor of the protocol and wrote the first draft of the manuscript. ES developed the idea and rationale for the study. SA designed the study. JAAS provided statistical inputs. KT contributed with scientific evidence regarding digital psychiatry. HB provided healthcare technology perspective and insight. All authors revised and approved the final manuscript.

Acknowledgments

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**Supplementary Materials**

Independent t-tests comparing change scores between the IP and VC groups and analyses of covariance (ANCOVA) after adjusting for baseline test scores. (Supplementary Materials)

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