Implementing a digital solution for patients with migraine - developing a methodology for comparing digitally delivered treatment to conventional treatment: A study protocol

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Study protocol

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Abstract

Background

Migraine is one of the most frequent and expensive neurological disease in the world. Non-pharmacological and digitally administered treatment options have long been used in the treatment of chronic pain and mental illness. Digital solutions increase the patients’ possibilities of receiving evidence-based treatment even when conventional treatment options are limited. The main goal of the study is to assess the efficacy of interdisciplinary digital interventions compared to conventional treatment.

Methods

The maximum number of participants in this multi-centre, open-label, prospective, randomised study is 600, divided into eight different treatment groups. The participants take part in either a conventional or a digital intervention, performing various tests and interdisciplinary tasks. The primary outcome is a reduction in the number of headache days. We also measure various other headache-related burdens as a secondary outcome.

Discussion

Based on preliminary data from the pilot study, digitally mediated treatment reduces a specialist's time spent on a single patient by more than tenfold. The sample size; digital interventions not conducted via video calls; a lack of human connection; limited intervention programmes and conducting studies only in digitally sophisticated countries are all significant limitations. However, we believe that digitally mediated treatment options are at least as effective as traditional treatment options while also allowing for a significantly higher patient throughput. The future of chronic disease treatment is remote monitoring and high-quality digitally mediated interventions.

Registration:

The study is approved by the Ethics Committee of the University of Tartu for Human Research (permission no 315T-17, 10.08.2020) and is registered at ClinicalTrials.gov: NTC05458817 (14.07.2022)

1. Background

Migraine as a global health problem

The prevalence of migraine in the adult population of the world is around 12% (1) in Europe 14,7% (2) and in Estonia 17,7% (3). Migraine is one of the most expensive diseases in the world, annually costing the European economy 95 billion Euros. Migraine sufferers miss between 2 and 46 days of work annually (absenteeism). Presenteeism, which reduces workability, productivity, and efficiency, is high in migraine sufferers and, as such, harms the economy (1, 4, 5).

Effectiveness of non-pharmacological interventions in migraine treatment

In addition to pharmacological treatment options, patient participation, self-help skills, and non-pharmacological interventions (NI) (patient education, headache nurse counselling, cognitive-behavioural therapy, and physiotherapy) are all essential parts of migraine treatment (6–11).

As NI, headache nurses provide patient education and counselling that has shown positive effects on the functioning of migraine patients (8, 9). Kristi Tamela's MSc thesis in Estonia emphasises the remarkable improvement in patients' quality of life within six months after receiving counselling from a headache nurse (10).
Relaxation techniques, progressive muscle relaxation, biofeedback, and cognitive-behavioural therapy (CBT) were formerly considered Level A therapies with an excellent safety profile (12, 13). Nevertheless, the 2019 Cochrane systematic review of psychological therapy for migraine prevention in adults found that there was not enough high-quality data to determine whether psychological therapies are effective (14).

The efficacy of physiotherapy, another NI component, varies depending on the headache diagnosis. The results concerning the efficacy of physiotherapy in the treatment of migraine are particularly contradictory. Physiotherapeutic treatment aims to reduce peripheral and central hypersensitivity, ease neck-shoulder strain, and reduce pain and vestibular symptoms (15, 16).

Although NI are a promising addition to medication, these interventions require more resources and are not universally accessible to migraine patients.

**Existing technology-based interventions**

In the current digital society, technology-based treatment alternatives are a powerful tool that help monitor the health status of a patient, organise and implement interventions, administer exchanges between healthcare providers, as well as support and treat patients with chronic diseases and mental health problems (17–19). Digital solutions have a great potential of increasing access to education, counselling, and self-help and providing NI for patients whose motivations and involvement in treatment may be limited by time, money/finances, or access to transportation (20–30).

Although some digital solutions are already used in the treatment of migraine, there is still room for improvement. There is a preponderance of research on the applicability of digital diaries. There is little information on comprehensive interdisciplinary digital NI and its effectiveness (31).

One of the most popular current mobile application that helps to monitor migraine is Migraine Buddy©, which records headache days, and tracks headache triggers, patterns, coping tactics, and more (32). Similar digital headache diaries (DHD) and assistants can monitor migraines and train health-related habits with minimal data loss, over 80% compliance, user-friendly solutions, patient acceptance, and a low perceived burden on daily life (33).

Digital CBT has been shown to be successful in the treatment of mood and anxiety disorders and can be used to ease similar accompanying emotional difficulties in people with migraine (34–36). According to recent studies, digital CBT has been found feasible, acceptable and efficacious in treating insomnia caused by chronic migraine and supporting migraine patients in emergency departments. The use of digitally administered relaxation techniques have also seen success (37–39).

Several chronic diseases can be treated with digital physiotherapy. An online programme is more cost-effective, allowing patients to learn and sustain physical activity while using interdisciplinary treatment concepts based on current treatment guidelines (40, 41).

Few studies have explored the efficacy of chatting with a headache nurse, virtual nurses, or virtual agents. Help4Mood uses a virtual avatar to help treat depression (42). Virtual nurses can collect medical data, assist patients, motivate them, and improve treatment adherence (43).

Several authors have concluded that in NI, the creation of an effective, novel, and evidence-based digital therapeutic (DTx) platform would improve patient self-management (44, 45). To our knowledge, there are no published articles on comprehensive digital intervention programmes of migraine.
Some issues with technology-based interventions

Much of the studies on technology-based interventions (TBI) and apps for chronic disease prevention and treatment mainly focus on application applicability, functionality, user experience, and desirable attributes. It is less known whether and to what extent applications are effective in achieving long term behavioural change (20–30).

Concerning digital solutions, the following have been highlighted as essential issues: a lack of real-time therapist/patient interaction; issues with providing personalised and timed feedback to participants; difficulties delivering TBI to patients; regionally variable availability of digital solutions; difficulties creating reports or summaries of the interventions of the patient; data protection issues; data loss due to technical, internet connection, programme compatibility, software or hardware issues (15, 30, 43).

As the treatment of headaches is complex and includes a combination of pharmacological and non-pharmacological treatments, preventative methods, lifestyle changes, and self-monitoring, treatment adherence is one of the major challenges of digital solutions (46, 47). According to previous research, the average user may abandon digital CBT after the first session due to the difficulty of maintaining treatment adherence with minimal or without any clinical contact (45, 48). Internet based CBT studies of depression state that the dropout rate is affected by the depression severity. Therefore, constant monitoring of depression and anxiety is required (49). Further studies are needed to evaluate the impact of anxiety and depression on the treatment adherence of a headache patient. Also, it is unknown whether evidence-based digital therapies can successfully be used outside of clinical practice (i.e., self-help with minimal or without any clinical intervention) (45, 46).

DHDs are essential for data collection, but their effectiveness compared to conventional “paper-pencil” headache diaries (PD) is unknown. It remains unclear whether DHDs enhance treatment adherence and which factors play an important role in treatment adherence.

In the PD, the patient often either pre-fills or writes the condition later (50–52). According to prior studies, the age, gender, season, day of the week, headache frequency, headache severity, headache medication use, and DHD completion time may all influence the diary filling adherence of the patient (51). Thus, which elements, background factors and other reminders influence DHD completion need to be identified in the present study.

The future direction is to specify the extent of which electronic behavioural interventions help reduce pain intensity and psychiatric symptoms. No study has been done on the “optimal dose” of behavioural interventions, such as the number of CBT sessions required, the best length of a CBT session, or when lessons/sessions should be altered (45). Also, the question arises whether evidence-based CBT is effective and can successfully be applied digitally with minimal clinical involvement.

So far, only a few studies have been conducted on virtually mediated nurse counselling and physical therapy. A completely virtual nurse (avatar) may be able to bridge the gap between health care possibilities and demands (long waiting lists, more demand than available specialists, cost-effectiveness), but it is unable of making diagnoses or collaborating with other team members (43). Good opportunities for nurse counselling sessions and enhancing clinical contact in digitally mediated interventions can be provided by counselling with nurses via online chatrooms. Still, there are a lot of limitations and problems to overcome (53). To our knowledge, the efficacy of digital physiotherapy and its usage in interdisciplinary headache treatment has not been studied.

2. Methods and design
2.1 The main goal and importance of the research

The main goal of the present study is to assess the efficacy of interdisciplinary digital interventions compared to conventional treatment options.

The essential secondary objectives include evaluating all intervention components both individually and in different combinations. Adherence, credibility, clinical contact, patient and specialist satisfaction, and the cost-effectiveness of digitally administered interventions are also compared with the conventional format.

There is a global shortage of clinical psychologists, CBT therapists, physiotherapists, and headache nurses. The shortage considerably contributes to the long waiting lists, the general limited availability of such specialists to headache sufferers, and the inconsistent availability of services. Geographic limitations are another common problem: patients who live far from larger centres have difficulties accessing services. Digital nurse counselling, CBT, and physiotherapy expand patient access to services while retaining adequate professional intervention methods (including real-time chatrooms). These digital solutions reduce dropout and improve intervention efficacy.

2.2 Study design

This is a multi-centre, open-label, prospective, randomised, and controlled study on the interdisciplinary intervention of migraine with digital technology-mediated treatment options versus conventional treatment options.

The procedures and design of the study were approved by the Ethics Committee of the University of Tartu for Human Research (permission no 315T-17) and the study is registered at ClinicalTrials.gov: NCT05458817.

In the preparation phase of the study, migraine patients and specialists from Estonia contributed to the project. They assessed the Migraine Buddy© application (32) and found it to be overly difficult, especially during the aura and attack phases of a migraine. The data of the application must also be available to specialists and compatible with e-health.

While preparing and planning the study, it became clear that there is no interdisciplinary digital solution for the treatment of headaches. Existing solutions are mostly digital headache diaries with individual appendices. There is no solution that allows to bring a comprehensive treatment including nurse counselling, psychotherapy and physiotherapy, to the patient.

In 2020, Migrevention© started developing an interdisciplinary mobile application and specialist dashboard for migraine patients. They conducted validation interviews with Estonian migraine patients before developing the digital solution. Validation interviews showed that patients are ready to implement digital education, CBT, and physiotherapy programmes into their treatment plan. The development of the Migrevention© application provided a good opportunity to study a digitally mediated interdisciplinary headache treatment and compare it with conventional treatment options. For that reason, we use the Migrevention© application, which allows the monitoring of the patient's use of the system, obtaining information about patients' preferences, their health behaviour, the actual application of patients' self-help skills, their needs for clinical intervention, etc. The digital format allows for reminders and a follow-up on patients, allowing researchers or clinicians to monitor data in real-time. The importance of this has also been emphasised in previous studies (54).

2.3 Planned sample size

In order to design the sample size, we conducted an estimated power analysis to establish the size of the groups (75 patients in each group) and strive for 80% power. Hence, the maximum estimated number of participants is 600.
The sample comprises of consecutive migraine patients who meet the inclusion criteria and visit a neurologist in partner clinic. In section 2.5, the precise involvement of patients is outlined.

**Consent to participate**

in the research is voluntary and does not affect the patient's possibility of using the Migrevention© solution or their usual minimal treatment options.

### 2.4 Participants inclusion and exclusion criteria

**Inclusion criteria:**

1. diagnosis of frequent episodic migraine, headache days per month 4–14 days;
2. patients aged 18–64 years;
3. very good command of the Estonian language both orally and in writing.

**Exclusion criteria:**

1. all other diagnoses of primary and/or secondary headaches;
2. currently existing severe depression;
3. history of psychotic disorder(s);
4. pregnancy or lactation;
5. severe somatic disorder(s);
6. history of severe organic psychiatric disorder(s);
7. history of other chronic pain condition(s);
8. history of addictive disorder(s).

### 2.5 Primary outcome measure

The primary outcome measure is a reduction of headache days (data derived from diaries) three months after the end of the interdisciplinary intervention programmes compared to the baseline (at the start of intervention).

### 2.6 Secondary outcome measures

The secondary outcome measures are as follows: number of headache days six and nine months after finishing intervention (follow-up) (data derived from diaries); consumption of analgesics or triptans (data derived from diaries); change in pain intensity (data derived from diaries); changes in depression, anxiety scores (data derived from tests); increase in pain acceptance (data derived from tests); changes in quality of life (data derived from tests); changes in number of sick-leave days (data derived from the national e-health system); impact on the burden of migraine assessed through sick-leave days, the disability rate, and specialists visits (data derived from e-health systems). Specific methods are presented in Table 1 and Table 2.
<table>
<thead>
<tr>
<th>Indicator</th>
<th>Method</th>
<th>Time</th>
<th>Procedures for use</th>
<th>Patient time for filling test</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of headaches</td>
<td>Digital diary, paper diary</td>
<td>Continuous</td>
<td>Continuous</td>
<td>&gt;2 minutes</td>
<td>Patient independently in the application or on paper</td>
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<tr>
<td>Medication use</td>
<td>Digital diary, paper diary</td>
<td>Continuous</td>
<td>Continuous</td>
<td>&gt;2 minutes</td>
<td>Patient independently in the application or on paper</td>
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<tr>
<td>Medication use</td>
<td>Prescription Centre</td>
<td>Continuously/Intervals</td>
<td>Continuously/Intervals</td>
<td>N/A</td>
<td>Specialist desktop/doctor or nurse.</td>
</tr>
<tr>
<td>The effect of headaches on everyday life</td>
<td>Headache Impact Test (HIT-6) (1)</td>
<td>Intervals</td>
<td>Intervals</td>
<td>2–5 minutes</td>
<td>The patient performs independently in the application or the test environment REDCap.</td>
</tr>
<tr>
<td>Screening for mental disorders</td>
<td>Emotional State Questionnaire (ESQ-2) (2)</td>
<td>Intervals</td>
<td>Intervals</td>
<td>2–5 minutes</td>
<td>The patient performs independently in the application or the test environment REDCap.</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) symptom checklist + Psychiatrist consultation (if DSM-V symptom checklist detects a mental health disorder)</td>
<td>Intervals</td>
<td>Intervals</td>
<td>60 minutes</td>
<td>The patient performs independently in the application or the test environment REDCap and/or one psychiatrist appointment</td>
</tr>
<tr>
<td>Personality profile</td>
<td>Swedish Universities Scales of Personality (SSP) (3)</td>
<td>Once at the beginning of the study</td>
<td>Once at the beginning of the study</td>
<td>30 minutes</td>
<td>The patient performs independently in the the test environment REDCap.</td>
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<tr>
<td>Indicator</td>
<td>Method</td>
<td>Time</td>
<td>Procedures for use</td>
<td>Patient time for filling test</td>
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<tr>
<td>Pain acceptance</td>
<td>Chronic Pain Acceptance Questionnaire-Revised (CPAQ-R) (4)</td>
<td>Intervals 3</td>
<td>Intervals 3</td>
<td>2–5 minutes</td>
<td>The patient performs independently in the application or the test environment REDCap.</td>
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<tr>
<td>Pain-related anxiety</td>
<td>Pain Anxiety Symptoms Scale (PASS) (5)</td>
<td>Intervals 3</td>
<td>Intervals 3</td>
<td>2–5 minutes</td>
<td>The patient performs independently in the application or the test environment REDCap.</td>
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<tr>
<td>Quality of life</td>
<td>EUROHIS-QOL 8-item index (6)</td>
<td>Intervals 2</td>
<td>Intervals 2</td>
<td>2–5 minutes</td>
<td>The patient performs independently in the application or the test environment REDCap.</td>
</tr>
<tr>
<td>Patient satisfaction with treatment</td>
<td>Headache Attributed Lost Time (HALT) (7,8), Headache Under-Response to Treatment (HURT) (7)</td>
<td>Intervals 3</td>
<td>Intervals 3</td>
<td>2–5 minutes</td>
<td>The patient performs independently in the application or the test environment REDCap.</td>
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<tr>
<td>Patient satisfaction with digital therapy</td>
<td>Satisfaction questionnaire</td>
<td>Intervals 3</td>
<td>Intervals 3</td>
<td>&gt; 2 minutes</td>
<td>The patient performs independently in the application or test environment REDCap.</td>
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<tr>
<td>Specialist satisfaction with digital treatment methods</td>
<td>Satisfaction questionnaire</td>
<td>Intervals 3</td>
<td>Intervals 3</td>
<td>&gt; 2 minutes</td>
<td>The specialist performs independently in the test environment REDCap.</td>
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<td>Indicator</td>
<td>Method</td>
<td>Time</td>
<td>Procedures for use</td>
<td>Patient time for filling test</td>
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<tr>
<td>Cost-effectiveness</td>
<td>Queries from the statistical databases of the Estonian Health Insurance Fund, the Social Insurance Board, and the Institute for Health Development</td>
<td>Intervals (^2)</td>
<td>Intervals (^2)</td>
<td>N/A</td>
<td>Health economist</td>
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<tr>
<td>Patient’s willingness to pay for headache treatment</td>
<td>Willingness to pay bidding game</td>
<td>Intervals (^2)</td>
<td>Intervals (^2)</td>
<td>2–5 minutes</td>
<td>The patient performs independently in the application or the test environment REDCap.</td>
</tr>
<tr>
<td>Demographics</td>
<td>Demographic Questionnaire</td>
<td>At the beginning of the study</td>
<td>Once at the beginning of the study</td>
<td>&gt;2 minutes</td>
<td>The patient performs independently in the application or the test environment REDCap.</td>
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</table>

\(^1\)At intervals - at the beginning of the study, at 8-week intervals, at the end of the study

\(^2\)At intervals - at the beginning of the study, at the end of the study

\(^3\)At intervals - at the beginning of the study, at the end of the study, in a follow-up study

References:


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<tr>
<th>Indicator</th>
<th>Method</th>
<th>Time</th>
<th>Procedures for use</th>
<th>Patient time for filling test</th>
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<tr>
<td>Method</td>
<td>Collected data</td>
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<tr>
<td>Participant demographics</td>
<td>Gender, age, place of residence, nationality, education, marital status, employment, income</td>
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<tr>
<td>Emotional State Questionnaire (EST-Q) test results</td>
<td>Subscales for depression, generalised anxiety disorder, panic disorder, insomnia, and asthenia</td>
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<tr>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) symptom checklist results</td>
<td>Depression, anger, mania, anxiety, somatic symptoms, suicidal ideation, psychotic symptoms, sleep problems, memory problems, compulsive thoughts and behaviours, dissociation, personality dysfunction, and drug use</td>
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<tr>
<td>EUROHIS QOL-8</td>
<td>Quality of life, satisfaction with health, satisfaction with the ability to do everyday life activities, satisfaction with oneself, satisfaction with personal relationships, satisfaction with living conditions, is there enough energy for daily activities, is there enough money to meet one's needs</td>
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<tr>
<td>Headache Impact Test (HIT-6)</td>
<td>Effect of headache on patient life</td>
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<tr>
<td>Headache Attributed Lost Time (HALT)</td>
<td>Loss of time due to headache</td>
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<tr>
<td>Headache Under-Response to Treatment (HURT)</td>
<td>Response to treatment</td>
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<td>Pain Anxiety Symptoms Scale (PASS)</td>
<td>Pain-avoiding behaviour, frightening thoughts, cognitive anxiety, physiological reactions to anxiety</td>
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<tr>
<td>Chronic Pain Acceptance Questionnaire-Revised (CPAQ-R)</td>
<td>Participation in activities, pain tolerance, pain acceptance</td>
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<td>Swedish Universities Scales of Personality (SSP)</td>
<td>Somatic trait anxiety, psychic trait anxiety, stress susceptibility, lack of assertiveness, impulsiveness, adventure-seeking, detachment, social desirability, embitterment, trait irritability, mistrust, verbal trait aggression, physical trait aggression</td>
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<td>Willingness to pay questions (WTP)</td>
<td>Willingness to pay for headache treatment</td>
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<td>Method</td>
<td>Collected data</td>
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<tr>
<td>Patient Satisfaction Questionnaire</td>
<td>Satisfaction with mobile application; Satisfaction with mobile application design (UI); Satisfaction with patient mobile application user experience (UX); Satisfaction with patient mobile application structure; Satisfaction with patient mobile application possibilities; information about the extent to which the mobile application facilitated the subject’s communication with the specialist; satisfaction with digital treatment compared to conventional treatment; whether digital treatment interventions could completely replace conventional treatment; whether the patient wants to continue using the patient application; what suggestions are made to improve the application; what other features patients want to see in the mobile application</td>
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</tr>
<tr>
<td>Specialist Satisfaction Questionnaire</td>
<td>Satisfaction with the specialist desktop; whether the desktop makes work easier; satisfaction with the specialist desktop design (UI); satisfaction with specialist desktop user experience (UX); satisfaction with the logic of specialist desktop; satisfaction with specialist desktop possibilities; whether the desktop facilitates communication with patients; whether the digital intervention has improved patient satisfaction with the service; what suggestions are made to make the desktop better; what other features you want to see in the mobile app</td>
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### 2.7 Patient’s inclusion and specialist’s involvement process

The neurologist examines the eligibility of the patient for the study, explains their opportunity to join the study, and delivers an informed consent form. Within three business days, the study team contacts the patient, provides answers for patient questions, asks patients to sign the informed consent form digitally, and conducts a randomisation. Subjects are divided among 8 different groups according to randomisation, and the treatment intervention continues according to the manual.

For digitally administered intervention, a separate desktop (Migrevention Clinical specialist dashboard) is developed for the specialists, which is accessible the work-computer of the specialist and is cross-linked to the mobile application of the patient (Migrevention Clinical). Specialists who treat participants via the Migrevention© digital solution are assigned a separate working time and a so-called remote reception time.

The usual clinical eye-to-eye contact during a conventional treatment intervention occurs as regular consultation according to a detailed intervention plan.

Clinical eye-to-eye contact during a digital treatment intervention occurs through video consultation if a specialist recognises the urgent need for it (for example, the depressive and/or anxiety scores of the patient increase).

### 2.8 Settings and randomisation process

The study is conducted in parallel for different intervention settings - the four study groups (digital treatment groups) and the four control groups (standard interdisciplinary treatment groups or treatment standard groups) (Table 3).
### Table 3
Division of groups

<table>
<thead>
<tr>
<th>Study group I</th>
<th>Control group I</th>
<th>Study group II</th>
<th>Control group II</th>
<th>Study group III</th>
<th>Control group III</th>
<th>Study group IV</th>
<th>Control group IV</th>
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</thead>
<tbody>
<tr>
<td>UMT&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>UMT</td>
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<tr>
<td>DHD&lt;sup&gt;2&lt;/sup&gt;</td>
<td>PD&lt;sup&gt;3&lt;/sup&gt;</td>
<td>DHD</td>
<td>PD</td>
<td>DHD</td>
<td>PD</td>
<td>DHD</td>
<td>PD</td>
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<tr>
<td>DHN&lt;sup&gt;4&lt;/sup&gt;</td>
<td>UHN&lt;sup&gt;5&lt;/sup&gt;</td>
<td>DHN</td>
<td>UHN</td>
<td>DHN</td>
<td>UHN</td>
<td>DHN</td>
<td>UHN</td>
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<tr>
<td>dCBT&lt;sup&gt;6&lt;/sup&gt;</td>
<td>uCBT&lt;sup&gt;7&lt;/sup&gt;</td>
<td>dCBT</td>
<td>uCBT</td>
<td>dPT</td>
<td>uPT</td>
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</tbody>
</table>

<sup>1</sup> UMT – Usual Minimal Treatment  
<sup>2</sup> DHD – Digital Headache Diary  
<sup>3</sup> PD – Paper Diary  
<sup>4</sup> DHN – Digital Treatment by Headache Nurse  
<sup>5</sup> UHN – Usual Treatment by Headache Nurse  
<sup>6</sup> dCBT – Digital CBT Program  
<sup>7</sup> uCBT – Usual CBT Program  
<sup>8</sup> dPT – Digital Physiotherapy  
<sup>9</sup> uPT – Usual Physiotherapy

After the initial informed consent, patients who are qualified for the study will be added to the research group and assigned a participation number based on the precise time the study group acquired the contact information of the patient (date and time if necessary). After informed consent is signed, participants are randomised into eight different groups. A randomisation table has been created for this purpose, in which 600 distinct numbers are randomly separated into eight groups. The patient is assigned to a group in accordance with the randomisation table.

All groups receive the usual minimal treatment consisting of medications in addition to the usual appointment with a neurologist. Control groups receive the usual treatment consisting of medications, the usual appointment with a neurologist, headache nurse, CBT therapist and a physiotherapist, in different combinations. All “as usual” treatments involve clinical eye-to-eye contact.

All participants of the study groups receive digital treatment consisting of medications and neurologist appointment as usual. Additionally every participant is assigned digital appointments to the following specialists: headache nurse, CBT therapist and/or physiotherapist. These appointments are assigned in different combinations, depending on the randomisation. The digital interventions are delivered through the Migrevention Clinical solution.

#### 2.9 Data collection

Data collection occurs digitally in the mobile application, in the online research environment REDCap of the National Centre for Transitional Medicine and Clinical Research, and at specialist receptions in parallel. The amount of data
collected varies from group to group and depends on the randomisation. Participants in the digital group complete the tests in the mobile application of the patient and in the REDCap environment. Participants in the control group fill in the tests and the satisfaction questionnaire in the REDCap environment. Specialists fill in the satisfaction questionnaire in the REDCap environment.

In addition to the data from tests and databases, the following data will be collected:

1) frequency of headache days; 2) pain intensity; 3) used medications; 4) performance of tasks sent or set by the headache nurse; 5) performance of the tasks sent or set by a CBT therapist; 6) performance of the tasks sent or set by a physiotherapist.

During the research, several parameters are measured, and the longest time is devoted to the patient’s completion of the tests at the beginning and end of the study 2-2.5h. The time required to complete the tests each week is between 5–10 minutes. The methods used in the study are presented in more detail in Table 2. The testing data collected in all groups is presented in Table 3.

### 2.10 Interventions

The NI conducted with the participants are detailed in Table 4. All materials that are sent to participants through the Migrevention Clinical solution (study group) or explained in a face-to-face appointment (control group) are based on the intervention manual and are the same in both groups. The discussion topics and the materials are distributed in the order specified in the intervention manual. Since the study attempts to mimic a standard conventional intervention as closely as possible, in case of conventional treatment (control group), the communication between the specialists and participants is not precisely described in the intervention manual, leaving each specialist free rein over communication.
Table 4
Interventions by group

<table>
<thead>
<tr>
<th>Study group (digitally mediated NI)</th>
<th>Control group (conventionally mediated NI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache diary</td>
<td>Participant is filling DHD in the Migrevention Clinical mobile application.</td>
</tr>
<tr>
<td></td>
<td>Participant is filling PHD, usually used in conventional treatment.</td>
</tr>
<tr>
<td>Headache nurse counselling</td>
<td>The headache nurse sends self-help materials (previously recorded audio) to the participant through the Migrevention Clinical specialist dashboard and communicates with the patient through the chatroom connected to the Migrevention Clinical mobile application.</td>
</tr>
<tr>
<td></td>
<td>The headache nurse arranges face-to-face meetings with the participant to provide conventional nurse counselling.</td>
</tr>
<tr>
<td></td>
<td>Meetings take place only at agreed times.</td>
</tr>
<tr>
<td>Cognitive-behavioral therapy</td>
<td>The clinical psychologist sends CBT based self-help materials (previously recorded audio), diaries (previously built-in) and exercises (previously recorded audio), through the Migrevention Clinical specialist dashboard.</td>
</tr>
<tr>
<td></td>
<td>The clinical psychologist arranges face-to-face meetings with the participant to provide conventional CBT.</td>
</tr>
<tr>
<td></td>
<td>Meetings take place only at agreed times.</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>The physiotherapist sends self-help materials (previously recorded audio) and exercises (previously recorded video) through the Migrevention Clinical specialist dashboard.</td>
</tr>
<tr>
<td></td>
<td>The physiotherapist arranges face-to-face meetings with the participant to provide conventional physiotherapy.</td>
</tr>
<tr>
<td></td>
<td>Meetings take place only at agreed times.</td>
</tr>
</tbody>
</table>

2.11 Statistical analysis

The programmes SPSS and R are used for data analysis. The use of the main generalised linear models for data analysis, such as ANOVA, MANOVA and multinomial linear regression analysis, are planned.

2.12 Ethics and approvals:

All patients wishing to participate in the study will be given a written informed consent form to read during their first appointment with their neurologist. Patients have the right to refuse to participate in the study, to suspend their
participation in the study, and to prohibit the use of their data in the study at any time.

On the digital platform and in the REDCap online environment, the data is collected in a personalized form. After the end of the personal intervention and the data quality control, personal data are separated from the survey data. The data is exported from the research server (server of the National Centre for Transitional Medicine and Clinical Research, Quretec server) to a computer for data processing (Microsoft Office Excel). All data is analysed in confidence with personal users and only for the purposes of this research under the Personal Data Protection Act (55). The data is stored in a digital form on the server of the National Centre for Transitional Medicine and Clinical Research (REDCap online environment) and the server of Quretec OÜ (digital platform). For data processing, the data is downloaded to the computer (Microsoft Office Excel) in an encrypted form. The code key is in a folder encrypted by the responsible researcher in the Tartu University Hospital Neurology department, and only the responsible researcher has access to it. The planned retention period of the data and the code key is 30 years (until 12/2050), which will allow for longitudinal studies, follow-up analysis, and data quality control of the topic in the future, when necessary.

Potential risks associated with the study.

In the study, the participants are asked to complete questionnaires, some of which are not routinely used in the clinical assessment of this group of patients, thus placing a somewhat greater time burden on the study participants than on regular patients. No patients will be deprived of their medication during the study, their medication will not be affected in any way, and there will be no additional risks for the participants.

3. Discussion

The biggest strength of the study is that to our best knowledge it is a randomised controlled study of a novel standardised manual-based intervention that focuses, among other things, on monitoring compliance and compares fully digital intervention with conventional interdisciplinary NI. The study compares digitally mediated, NI migraine treatment options with conventional ones. It is designed by an interdisciplinary team, who participated in the designing of the multi-centre randomised control-study. The study compares interventions to discover the best way to improve patient health and quality of life, to save specialists’ time and to help more migraine patients. First, we conducted a small-scale pilot study. The main purpose of the pilot was to prepare for a large-scale study and to find the technical difficulties/processes that needed improvement. However, we already realised from a small-scale pilot study that a digitally mediated treatment reduces the time a specialist spends on a single patient by more than tenfold (56).

Another strength of the study is the assessment of the efficacy and applicability of each treatment component separately, in addition to the whole treatment protocol.

The authors hope that the study helps to overcome the difficulties in the field of digital therapeutics (DTx). The study provides an opportunity to begin to determine the effectiveness of DTx in the treatment of migraine. The implementation of the project also allows to contribute to finding out how to integrate DHD data with the e-health system so that is usable for all providers (including general practitioners) and how to link DHDs with electronic health records.

Interdisciplinary intervention in migraine treatment is known to be effective, especially in preventing migraine chronification. Given the high risk of migraine chronification, long-term treatment adherence and follow-up may be essential to ensure the long-term effectiveness of digital interventions. Based on the above, the research plans to conduct long-term follow-up studies (3, 6, 9 months after the end of the intervention).
There are some limitations that may affect the conduction and results of the study and must be considered when interpreting the results in the future.

The initial sample size will be at least 75 patients in each group, according to the Power analysis. Due to the time-consuming conventional interventions and the time needed to collect data, the realistic obtainable group size within the given timeframes of the study may be smaller. The study may favour the larger clinics and research centres to adopt the protocol and conduct the study and limit similar possibilities of smaller centres. In order to overcome this problem, interim analyses can be undertaken to examine statistically significant associations in a smaller number of patients.

Digital interventions, that are not conducted via video call, are unique strategies that may not be preferred by many individuals in certain situations. In digital interventions, the authors have planned patient initiated clinical contacts only via chatroom. Studies on whether and how much clinical contact is required are controversial (57, 58). The lack of human connection may affect patient adherence, increase the drop-out rate and limit treatment efficacy for some patients. The predetermined and limited number of techniques for use by the specialists may affect the flexibility of treatment. It must also be considered that the entire intervention programme is a minimum programme, and minimal intervention may not have enough power to prove the effectiveness of a NI migraine treatment.

The whole intervention that is done on Estonian patients is a limitation by itself. Estonia is a digitally advanced country whose residents use digital solutions daily. These settings may not be equivalent in other countries and cultures. Hence, the developed methodology is best applicable in countries with similar settings and, consequently, must be repeated in other countries with different settings.

The authors intend to demonstrate that digitally mediated treatment is at least as effective as conventional treatment but allows for a significantly higher patient throughput, saves/improves specialist workload and is cost-effective. Authors expect remote monitoring and high-quality digitally mediated interventions to be the future of chronic disease treatment.

**Abbreviations**

NI
non-pharmacological interventions

TBI
technology-based interventions

CBT
cognitive-behavioural therapy

DTx
digital therapeutics

DHD
digital headache diary

PD
paper headache diary

HIT-6
Headache Impact Test

ESQ-2
Emotional State Questionnaire

DSM-V
Declarations

Ethics approval and consent to participate: The study is approved by the Ethics Committee of the University of Tartu for Human Research (permission no 315T-17, 10.08.2020) and is registered at ClinicalTrials.gov: NTC05458817 (14.07.2022). Informed consent to participate will be obtained from all participants.

Consent for publication: Not applicable

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study protocol.

Competing interests: Authors Triinu Niiberg-Pikksööt and Mark Braschinsky are founders of Migrevention OÜ, which develops Migrevention Clinical mobile application and Migrevention Clinical specialist dashboard.

Author Anu Aluoja is participated as a consultant in creating CBT module in Migrevention Clinical mobile application.

Author Kariina Laas has no competing interests to declare.

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Authors’ contributions: TNP contributed to the development of the study protocol, writing the application of the ethics committee, is responsible for data collection according to the protocol, and writing the current manuscript. AA contributed to the development of the protocol and proof-reading of the current manuscript. MB contributed to the development of the protocol, writing the application of the ethics committee, registration in ClinicalTrials.gov databases, funding and proof-reading of the current manuscript. KL contributed to the development of the protocol and proof-reading of the current manuscript. All authors read and approved the final version of the manuscript.

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