Supporting patients' medication management using eHealth

Test cases in rheumatology

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"I've been going through something.
One thousand eight hundred and fifty-five days I've been going through something."

Kendrick Lamar/Bart Pouls

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Chapter 1

General introduction

Aim of this thesis

This thesis investigates how eHealth can be applied to support patients in managing their medication. To this end three eHealth interventions are studied that attend to medication administration, tele-monitoring disease activity or medication adherence. The eHealth interventions are tested in patients with inflammatory rheumatic diseases who serve as model for patients using long-term medication. This thesis aims to answer how patients experience these eHealth interventions and whether these eHealth interventions benefit medication management at home. In this general introduction the current challenges of patients' medication management, eHealth as a possible solution, challenges of its application and how this thesis addresses these challenges are outlined.

Appropriate use of medication in long-term conditions

Long-term conditions are most commonly prevented by or treated with medication.[1] In 2020 approximately 12 million Dutch people received medication from a pharmacy. Of these pharmacy visitors, 7.7 million (64%) used long-term medication defined as one or more medications that are prescribed for more than 90 days a year and 1.8 million (15%) are classified as polypharmacy patients using five or more different types of medications.[2]

Although pharmacotherapy is effective in treating health problems, improving quality of life and preventing mortality, achieving these outcomes is hampered by drug-related problems. Drug-related problems are all events or circumstances involving pharmacotherapy that actually or potentially lead to lack of effect or adverse drug events.[3] Drug-related problems occur frequently in patients using long-term medication, generally varying from 1 to 4 per patient at any given time point.[4–7] Due to drug-related problems only 42% of patients use medication errorfree.[8] The term drug-related problems is used to refer to a wide range of potential problems ranging from drug selection by healthcare providers to patient behaviour.[3] In this thesis focus is on drug-related problems at the patient level. Examples include administering medication incorrectly or using medication differently to what has been agreed upon with the healthcare provider.

Preventing drug-related problems and (thereby) optimising effectiveness of medication can lead to an increase in quality of life and a decrease in healthcare burden.[9–11] Patients have a need for support in medication management to prevent drug-related problems.[12] The number of potential drug-related problems is growing exponentially as the population ages and simultaneously uses more long-term medication.[11,13,14] Additional problem is that the healthcare provider workforce will not be able to keep up with the growing healthcare demand of the population.[15] Hence there are a lot more drug related problems to tackle and prevent for patients with less healthcare providers to help support them and there is a need for an efficient way to provide support for patients using long-term medication.

eHealth can facilitate patients' medication management

eHealth might facilitate medication self-management as this allows patients to engage at a convenient place and time and require minimal effort from healthcare providers. eHealth is defined as the use of information and communication technology in healthcare.[16] With such a broad definition, eHealth can take on many forms and serve anyone within healthcare, from patient to healthcare provider. In this thesis the end-user of eHealth is the patient and the purpose is to support patients in appropriately using their medication.

Most patients believe they can benefit from eHealth in some way (e.g. less time consuming, easily accessible) and think it can complement current practices.[17] Another advantage of eHealth is it can facilitate medication management by providing interactive interventions independent of time and location. eHealth interventions allow for interaction as patient input can determine intervention output. Such interaction can create continuous feedback loops and thus keep track of and help reflect on disease activity and medication-taking behaviour. As a result, eHealth interventions can support medication use in various ways, for example: provide and test medication knowledge, assist drug delivery, remind of medication intake or monitor disease activity. Despite these possible assets eHealth interventions come with challenges too.

Challenges of using eHealth

Just like medication, eHealth only works when applied and implemented properly. Currently eHealth is hardly regulated which has the advantage of allowing everybody to advance healthcare through use of technology but the disadvantage that there is no need to show effectiveness before 'market' access.[18–20] To ensure eHealth truly advances healthcare, is implemented and used, effectiveness should be thoroughly investigated.

Similarly, eHealth interventions do not work in patients who do not use them. Although intervention use is underreported and highly variable, uptake is positively associated with reaching the target outcome.[21] Actual intervention use is, in part, influenced by perceived usefulness and perceived ease of use according to the Technology Acceptance Model, a commonly used model for assessing eHealth interventions.[22–24] As patient acceptability is partly responsible for intervention uptake it is an important outcome when studying eHealth interventions. In addition, combination of demographic characteristics and acceptability outcomes can reflect if eHealth interventions are suited to encompass the full width of the target population. For example, if ease of use declines with age this might be an indicator that the intervention is less accessible to those with lower digital skills.[25] Even though eHealth can be advantageous and its use is on the rise, scientific evidence about usability and effectiveness is lacking.[18–20] To sum up, effectiveness and patient acceptability of eHealth interventions are vital aspects that so far remain underexposed in the 'open' eHealth market.

Inflammatory rheumatic diseases as model for long-term conditions

The need for supporting patients' medication management is most evident in long-term conditions as management of these conditions generally consists of long-term pharmacological treatment. Inflammatory rheumatic diseases are a prime example of this and serve as a model for application of eHealth interventions to support long-term medication use in this thesis. Inflammatory rheumatic diseases are immune-mediated long-term illnesses of the musculoskeletal system that have a component of inflammation leading to warm, swollen and tender joints.[26] In the Netherlands there are 220.000 people with inflammatory auto-immune disease and 370.000 people with gout. Most patients use medication in trying to achieve remission or combatting a disease flare (see table).[26–28] Disease-Modifying Anti-Rheumatic Drugs (DMARDs) are the cornerstone of inflammatory auto-immune disease treatment. DMARDs are effective in reducing disease activity and radiological progression and in increasing daily functioning in patients.[28–31] When – despite pharmacological treatment – disease activity flares, symptoms can be alleviated with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or prednisone. Gout flares can be treated with the same medication in addition to colchicine. If gout flares occur frequently it is advised to start with urate lowering agents to reduce the number of flares.[32]

Although patients may benefit from anti-inflammatory medication, there is a chance of downsides too. Patient interviews have taught us patients experience drug-related problems over-time such as medication concerns or (suspected) side-effects related to medication prescribed by the rheumatologist.[7] When untreated, drug-related problems can lead to clinical consequences such as an increase in morbidity and mortality.[8,33] Patients with inflammatory rheumatic diseases might benefit from support in medication management if it can reduce drug-related problems or the chance thereof. The eHealth interventions described in this thesis aim to support patients with rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis and gout in managing their medication (see table 1).

Table 1. Main characteristics of test cases in this thesis

eHealth intervention	Medication support	Inflammatory rheumatic disease	Studied in	Study outcomes
Electronic injection device	Medication use	Rheumatoid arthritis Axial spondylarthritis Psoriatic arthritis	Chapter 2	Patient satisfaction Patient preference
Daily query smartphone application	Monitoring disease	Gout	Chapter 3	Patient acceptability Technical feasibility Clinical feasibility
Serious puzzle game smartphone application	Medication adherence	Rheumatoid arthritis	Chapter 5 Chapter 6	Patient acceptability Intervention effectiveness

Outline of this thesis

Taking the above together, this thesis investigates how eHealth interventions can support patients with inflammatory rheumatic disease in using their long-term medication (see table 1). The eHealth interventions investigated in this thesis support patients in various ways:

An electronic self-injection device can support patients in correctly administering medication and in **Chapter 2** patient preference and satisfaction with this device are studied. The unpredictability of gout flares makes patients often have to initiate and discontinue medication which is investigated in **Chapter 3** on the feasibility of tele-monitoring gout flares using a smartphone application. Both chapters mainly focus on patient experiences of eHealth. Effectiveness of eHealth on medication adherence is subject of the rest of the thesis. First of all, a systematic review on eHealth interventions for improving medication adherence is performed in **Chapter 4**. Next the development of a serious game intervention for improving medication adherence is described in **Chapter 5**. And finally, effectiveness of the developed serious game is tested in a randomised clinical trial described in **Chapter 6**. In **Chapter 7** we put the findings of this thesis in perspective, discuss how findings relate to other patient populations and provide recommendations for clinical practice.

1

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Chapter 2

A Pilot Study Examining Patient Preference and Satisfaction for ava, a Reusable Electronic Injection Device to Administer Certolizumab Pegol

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Abstract

Background
Anti-tumour necrosis factor (anti-TNF) adherence is suboptimal. ava®, a reusable electromechanical self-injection device (e-Device) developed for certolizumab pegol (CZP) administration, aims to overcome some barriers to increase adherence.

Objective
This study evaluates patient experience of the e-Device and its training materials and determines patient device preference.

Methods
CZP-treated patients were recruited from the Netherlands, Denmark and Sweden. Patients completed a pre-injection Assessment of Self-Injection (ASI) questionnaire investigating self-injection perception. After training, patients administered 3 consecutive self-injections using the e-Device, patient experience of each was assessed using the post-injection ASI. An additional questionnaire evaluated training materials. After Injection 3, patients indicated their preference: the e-Device or their previous device.

Results
59 patients participated; most rated the e-Device highly for satisfaction, self-confidence and ease of use. The (negative) feelings and pain and skin reactions domains had low ratings. Post-injection ASI domain scores were similar following each of the 3 e-Device injections. Training materials were rated highly (video: 8.4/10; step-by-step guide: 8.4/10). 57.1% (32/56) patients preferred the e-Device over their previous self-injection device.

Conclusion
Patients were satisfied with the e-Device and most preferred it over other self-injection devices. By improving patient experience, the e-Device may help increase medication adherence.

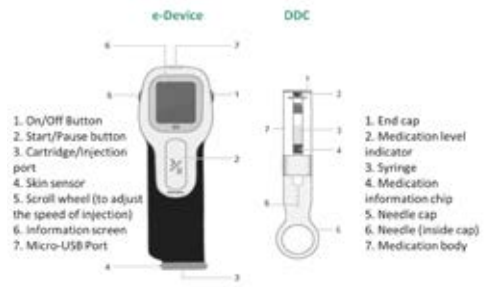
Introduction

Anti-tumour necrosis factors (anti-TNFs) are effective treatments for moderate to severe chronic inflammatory diseases, including rheumatoid arthritis (RA), axial spondylarthritis (axSpA), psoriatic arthritis (PsA), plaque psoriasis and Crohn's disease.[1–5] The majority of anti-TNFs are administered subcutaneously and can be self-injected by patients.[6,7] Self-injection allows more flexibility and independence as patients can administer their treatment in their home without the help of healthcare professionals (HCPs).[7,8] Regular trips to a hospital can be a burden for patients, both financially (e.g. travel costs, cost of taking time off work) and due to reduced mobility and high levels of fatigue.[9] By providing benefits for the patient, self-injection can also benefit caregivers, the healthcare system and society generally.[7]

Patients may encounter challenges when self-injecting anti-TNFs.[10,11] These can include patient needle phobia, a lack of confidence in their own ability to safely and effectively administer injections and remembering the dates of their self-injections.[10–12] As a result, adherence to anti-TNF treatment regimens is often suboptimal, negatively impacting patient outcomes and disease control.[13–15] Many patients with chronic inflammatory diseases are dependent on lifelong treatment to suppress joint damage and to avoid functional impairment. Tailoring self-injection devices to individual patient preference may improve patients' adoption of the device and, consequently, medication adherence.[10,16,17] Additionally, introducing more advanced technologies in the management of chronic inflammatory diseases provides a unique value proposition as this approach may advance patient engagement and empowerment.[18]

ava® is a new reusable electromechanical self-injection device (e-Device) designed for use with the anti-TNF certolizumab pegol (CZP).[19,20] It was developed in conjunction with OXO (New York, NY, USA) and with patients, to help personalise their self-injection experience. The e-Device includes a range of features to improve patient experience of self-injection (Figure 1).[21] This study is the first to report the use of the e-Device in a real-world setting and investigate its usability for patients treated with CZP in clinical practice. Secondly, this study aimed to investigate the patient experience of self-injection both prior to and after using the e-Device. Patient preference for the e-Device compared to their current self-injection device was also determined. Finally, this study also aimed to evaluate training materials designed for patients using the e-Device.

A. CZP e-Device and dose-dispenser cartridge



B. Key features of the e-Device

Feature	Key aspects
GUI screen	• Step-by-step instructions • Advice and warning messages • Injection completion confirmation • Notification of next injection
Injection control	• Scroll wheel allows adjustment of injection speed to slowest/slow/fast/fastest • Option to pause injection with needle inside skin
USB port	• To charge the e-Device • To upload/download injection history to a computer
Training DDC	• Reusable DDC to practice injection process • No needle and no medication • GUI screen training guidance
Skin sensor	• Ensures contact with skin when injecting • Stops injection and retracts needle if e-Device removed from skin contact
Hidden needle	• Needle is inside the DDC; it is not visible during the injection procedure
Injection log	• Records if doses were delivered completely, incompletely or missed • Can be shared with HCP
Security	• Drug identity check • Expiry status check • Use status check

Figure 1. Diagram of the e-Device
Taken from CZP Summary of Product Characteristics. CZP: certolizumab pegol; DDC: dose-dispenser cartridge; GUI: graphical user interface; HCP: healthcare provider.

Methods

Study design

Data were collected before use of the e-Device and immediately after three consecutive injections using the e-Device. Injections were carried out two weeks apart (Figure 2). Patients initially answered the pre-injection Assessment of Self-Injection (pre-ASI) questionnaire to assess their feelings about self-injection and self-confidence at study baseline. Patients were then trained by an HCP to self-inject using the e-Device and given a step-by-step guide on the usage of the e-Device. In addition, patients were encouraged to watch a provided training video on self-injection with the e-Device. The next three injections in the patients' treatment regimen were administered using the e-Device at their homes, and are referred to as Injection 1, Injection 2 and Injection 3 (either the maintenance dose of 200 mg CZP every two weeks, or the loading dose of 400 mg CZP every two weeks). After administering each of the three injections, patients completed the post-injection Assessment of Self-Injection (post-ASI), to assess patient experience using the e-Device. In addition, patients answered questions about the training video and step-by-step guide, following their first or second injection. After the third injection, patients were asked their preference between the e-Device or the device(s) they had previously used for self-injection.

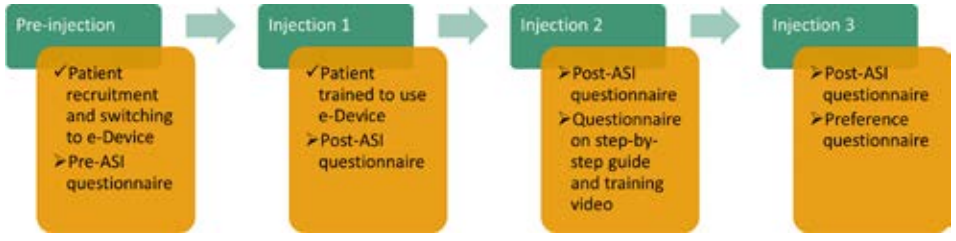


Figure 2. Study outline
A CZP self-injection with the e-Device was carried out by each patient at every two weeks. ASI: Assessment of Self-Injection; CZP: certolizumab pegol.

Patients

Patients treated with CZP were recruited from the Netherlands, Denmark and Sweden through three rheumatology clinics and gave signed informed consent to be included in the study. Patients were adults (aged between 18 and 85 years) with experience of self-injecting CZP and/or other biologics using either a pre-filled syringe (PFS) or a pre-filled pen (PFP) for RA, axSpA or PsA. Patients were excluded if they suffered from a visual impairment that made it impossible to read or complete the required questionnaires, or if they were not fluent in the language of the questionnaires.

Study evaluations

Patient experience of self-injection, both before and after using the e-Device, were measured using the ASI questionnaire. This questionnaire is a version of the Self-Injection Assessment Questionnaire modified to assess self-injection using an e-Device. The pre-injection ASI (pre-ASI) section comprised six preliminary questions split into two domains, '(negative) feelings about self-injection' and 'self-confidence'.[11] Questions asked patients about their feelings regarding needles and injections, and their self-assessment of their ability to correctly, cleanly and safely inject CZP.

After each injection, patients were asked to complete the post-ASI questionnaire comprising of 44 questions evaluating patients' experience of using the e-Device. These questions were grouped into six domains for which an overall domain score was calculated.[11] Domain themes included (negative) feelings, self-image, self-confidence using the e-Device, pain and skin reactions, ease of use and overall satisfaction with the e-Device.

Within the first two weeks of the study, patients also completed the implementation questionnaire comprised of 12 questions assessing patient opinions on the training materials provided with the e-Device. Patients rated the training video and step-by-step guide on whether they were easy to understand, detailed enough and interesting (training video) or useful (step-by-step guide). The final question about each training aid asked patients about the overall usefulness of the training materials. The implementation questionnaire also included open-ended questions to collect further information about patients' opinions on the training materials.

After the third injection, patients completed the preference questionnaire, answering nine questions on their preference for different CZP self-injection devices, including their overall preference. The questions of all questionnaires can be found in the Supplementary Materials.

Statistical analysis

Patients rated individual questions in the pre- and post-ASI questionnaires on scales of 0–4 or 0–5. To allow comparison between both questions and ASI domains, individual question scores were converted to a 10-point scale. ASI domain scores were calculated using the same method as used for the SIAQ: domains were calculated as the mean of the item scores included in the domain and were only calculated if at least half of the domain items were completed.[11]

Patients answered each question of the implementation questionnaire using a rating scale of 0–4, or 1–10 for the overall usefulness rating of the video or step-by-step guide. The mean score was calculated for each question. The number and percentage of patients rating the overall usefulness of the video or step-by-step guide highly (defined as a rating of 8, 9 or 10 out of 10) was also calculated. For the preference questionnaire, the number and percentage of patients for preferring each device was evaluated.

Results

Patient disposition and baseline characteristics

59 patients were eligible, provided written informed consent and entered the study across the three countries (Netherlands: 24, Denmark: 15, and Sweden: 20). Of the 59 included patients, 57 provided data across all three timepoints of the study. Pre- and post-ASI questionnaires were fully completed in Denmark and the Netherlands, however, in Sweden some questions were omitted; therefore, the overall post-ASI domain scores are reported for Denmark and the Netherlands only (n=39).

Patient characteristics are shown in Table 1. The mean age of patients was 55 years (standard deviation [SD]: 16 years) and 42/59 (71%) of patients were female. Overall, most patients were diagnosed with RA (38/59; 64%); the remaining patients had received either an axSpA or PsA diagnosis (9/59 [15%] and 12/59 [20%], respectively).

Table 1. Characteristics of the patients that used the e-Device

	All patients (n=59)	Netherlands (n=24)	Denmark (n=15)	Sweden (n=20)
Age (years), mean (SD)	55 (16)	49 (15)	54 (16)	61 (15)
Female gender, n (%)	42 (71)	22 (92)	6 (40)	14 (70)
Disease diagnosis				
RA, n (%)	38 (64)	15 (63)	9 (60)	14 (70)
axSpA, n (%)	9 (15)	3 (13)	4 (27)	2 (10)
PsA, n (%)	12 (20)	6 (25)	2 (13)	4 (20)

axSpA: axial spondylarthritis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SD: standard deviation.

Self-injection confidence – Results from Pre-ASI (Netherlands and Denmark, n=39)

In the pre-ASI, 5/39 (13%) patients stated they were 'very' or 'extremely' afraid of needles, 4/39 (10%) were 'very' or 'extremely' afraid of giving an injection and 4/39 (10%) stated they were 'very' or 'extremely' anxious about self-injecting. However, 33/39 (85%) felt 'very' or 'extremely' confident giving the injection in the right way. 35/39 (90%) patients, felt they were 'very' or 'extremely' confident giving injections both in a clean/sterile way and safely. Mean converted scores for all domains, both overall and for individual countries (including Sweden, where applicable), are shown in Figure 3.

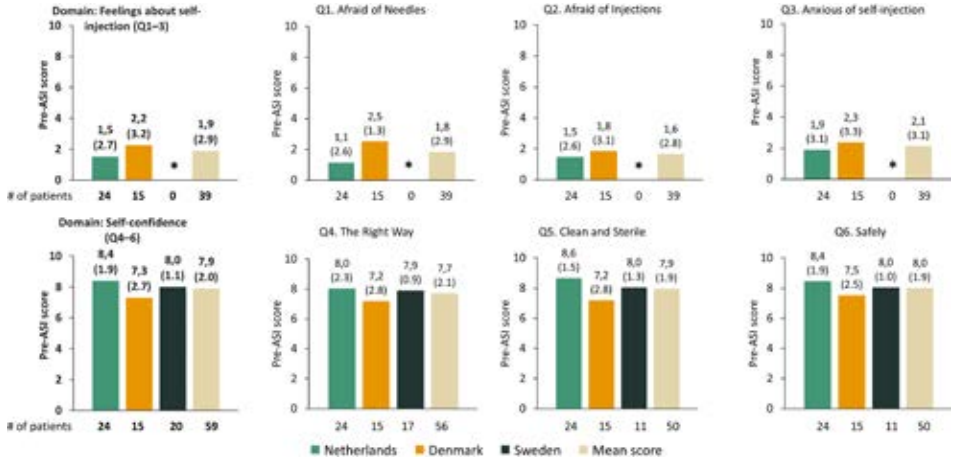


Figure 3. Mean patient responses to the pre-ASI.

* No data available for Sweden. # = number. Data labels indicate mean (standard deviation). Item scores were converted to a 10-point scale (0: not at all; 10: extremely). ASI: Assessment of Self-Injection.

Satisfaction and experience with the e-Device – Results from the post-ASI (Netherlands and Denmark, n=39)

Post-ASI domain scores were comparable following each injection and between countries (Figure 4). Further analyses of the individual questions in the post-ASI pain and skin reactions domain demonstrate that of the 10 questions asked, patients were most bothered by pain at the injection site, scoring this question highest in the domain, and least bothered by cold or itching, scoring these questions lowest (3.0/10 and 0.2/10, respectively; Supplementary Figure S1). There was very little between-injection variation in question scores in the pain and skin reactions domain. Additionally, there was no difference between the (negative) feelings about self-injection and self-confidence domain scores in the pre-ASI and post-ASI questionnaires ([negative] feelings about self-injection mean pre-ASI score: 1.6/10 vs. Injection 3 post-ASI score: 1.4/10; self-confidence mean pre-ASI score: 7.9/10 vs. Injection 3 post-ASI score: 7.8/10). Analysis of individual post-ASI questions answered by all three countries can be found in the Supplementary Materials (Supplementary Figures S2–5).

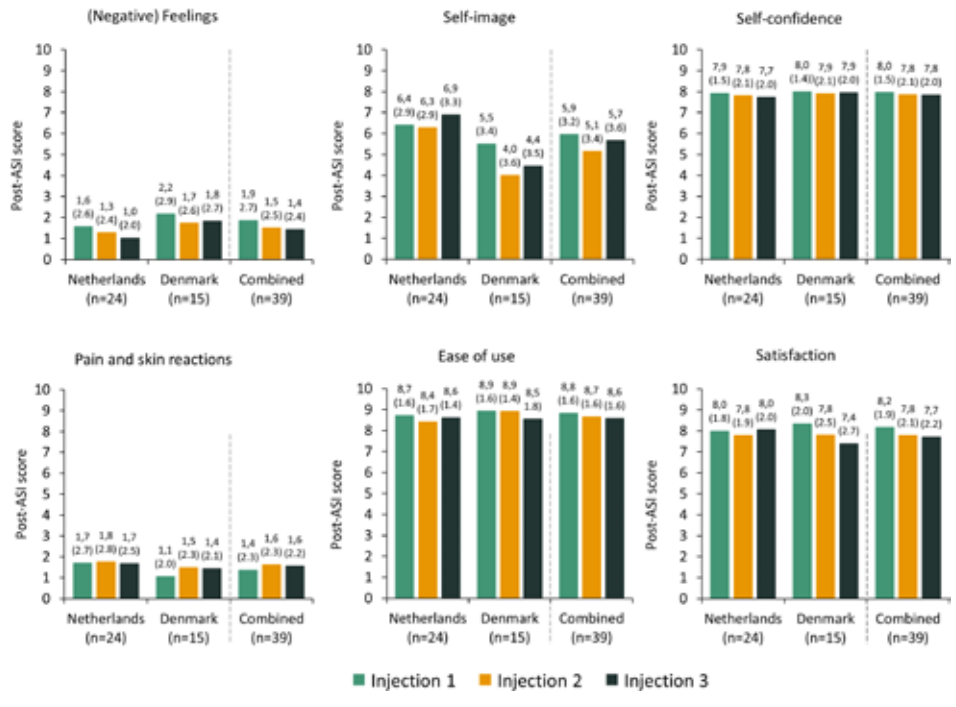


Figure 4. Mean post-ASI questionnaire domain scores in the Netherlands and Denmark.

Data labels indicate mean (standard deviation). Item scores were converted to a 10-point scale (0: not at all; 10: extremely) and the domain score was calculated as the mean of the item scores included in the domain. Domain scores were only calculated if at least half of the domain items were completed. ASI: Assessment of Self-Injection.

Patient preference for the e-Device (across all countries)

Overall, most patients preferred the e-Device to their previous CZP self-injection device(s) (32/56 [57%]; Table 2). 15/56 (27%) patients preferred the injection device they had previously used, and 9/56 (16%) patients had no preference for either device. Analysis of individual questions found that patients were most likely to select the e-Device as the easiest to hold (44/57; 77%), safe (41/57; 72%) and having the most control over the self-injection process (39/57; 68%). However, only 13/52 (25%) and 20/57 (35%) preferred the e-Device for travel and storage, respectively.

Table 2. Patient preference for different self-injection devices

Preference Question	n (%)			
	e-Device	PFS	PFP	No preference
Q1. Safe	41 (72)	10 (17)	1 (2)	5 (9)
Q2. Confident	33 (58)	12 (21)	3 (5)	9 (16)
Q3. Easy to hold	44 (77)	8 (14)	2 (4)	3 (5)
Q4. Control	39 (68)	13 (23)	0 (0)	5 (9)
Q5. Storage	20 (35)	19 (33)	5 (9)	13 (23)
Q6. Travel	13 (25)	20 (39)	8 (16)	10 (20)
Q7. Time	25 (45)	14 (25)	2 (4)	15 (27)
Q8. Convenience	35 (63)	9 (16)	3 (5)	9 (16)
Q9. Overall	32 (57)	14 (25)	1 (2)	9 (16)

PFP: pre-filled pen; PFS: pre-filled syringe.

Patient opinions of the e-Device training materials (across all countries)

The step-by-step guide and the training video were well received with 39/53 (74%) patients and 34/46 (74%) patients, respectively, rating the materials as highly useful (giving a score of 8, 9 or 10 out of 10). Scores for individual questions, both by country and overall, are presented in Supplementary Table S1. Patient comments highlighted that users found the training materials helpful ("I found the step-by-step guide very relevant and educational") and easily understandable ("The picture series tells more than clear instructions").

Examining the results by country, the step-by-step guide was ranked highly for overall usefulness in all countries (average rating in the Netherlands: 8.0/10 [n=24]; Denmark: 7.9/10 [n=15]; Sweden: 9.2/10 [n=20]). The training video was also ranked highly: average ratings were 8.4/10 in the Netherlands (n=24), 7.9/10 in Denmark (n=15) and 8.8/10 in Sweden (n=20).

Discussion

Overall, the e-Device was well received: patients found it easy to use and reported high levels of confidence and satisfaction. Furthermore, after three self-injections, most patients preferred the e-Device to their previous self-injection device(s).

Prior to e-Device use, a few patients rated themselves as anxious about needles and injections and, generally, patients were confident about their ability to self-inject, possibly due to their prior self-injection experience. Post-ASI questionnaire results indicate that patients had positive experiences using the e-Device. Satisfaction, self-confidence and ease of use domains were all consistently rated highly, both across countries and over time, corresponding to a positive self-injection experience with the e-Device. The pain and skin reactions domain was generally scored lowest compared to all other domains, and patients also reported low levels of negative feelings regarding e-Device use, again indicating a positive self-injection experience. High patient satisfaction reported with the e-Device indicates it may help address some of the challenges associated with self-injection, such as needle phobia and hand dexterity problems. Previous studies in RA patients have shown a general preference for a large grip as this aids drug administration for individuals with hand dexterity problems.[20,22]

Increased patient satisfaction has previously been shown to increase patient adherence.[22] Adherence to anti-TNFs for the treatment of chronic inflammatory diseases is known to be low (59% [95% confidence interval: 58–60%]),[13] which in turn can reduce disease control and long-term outcomes.[10,14] High patient satisfaction levels with the e-Device may lead to improved adherence and clinical outcomes. Forgetfulness has also been shown to influence patient adherence.[18] The e-Device notification of the next injection could help reduce non-adherence due to forgetfulness. Similarly, increasing patient control over treatment administration can facilitate patient empowerment.[23] Both device design, such as the ability to vary injection speed or pause an injection with the ava® e-Device, or patient development of habits and 'rituals' surrounding self-injection can help increase patient control. Together with increased patient confidence, this in turn can contribute to increased treatment adherence.[11,23]

After training and e-Device use, high levels of satisfaction with the step-by-step guide and training video were also reported. Providing step-by-step on-screen instructions has been shown to improve patient confidence in their ability to successfully complete a self-injection.[21] Patient responses to open-ended questions in the Implementation Questionnaire support this idea with multiple individuals commenting on the helpfulness and clarity of the on-screen instructions ("The picture series tells more than clear instructions"; "The information on the device is so good and relevant").

Fewer patients from the Netherlands responded to the questions referring to the training video in the implementation questionnaire compared to patients from Sweden and Denmark. This was due, in part, to fewer patients in the Netherlands watching the video as the video link did not work for some patients. Additionally, patient responses from all three countries suggested the on-screen instructions were so comprehensive that some patients did not feel they needed to watch the training video ("The animation video is not needed, the step-by-step guide is enough"; "I didn't watch the video because ava® is clear enough"), that the video was too long ("It takes a long time to watch and its quite long winded") or that the video was more

suitable for patients who had never self-injected before ("As a first-time user of biologics the video might also be a good idea – but for me it's too long").

Overall, the e-Device was the preferred device for most patients. This indicates that the e-Device may meet previously unmet needs of patients using self-injection devices. Patients were most likely to prefer the e-Device when asked about the self-injection process, for example, injection safety, control and ease. This finding may be expected as the e-Device was developed through multiple iterations of patients testing and evaluating its ability to aid successful self-injection.[21]

It should be noted that not all patients preferred the e-Device over their previous self-injection device. This suggests differences in the self-injection device features required and/or preferred by individual patients and supports previous research that found different patients place different values on the features of self-injection devices.[24] For example, previous research has suggested patients who prefer using a PFS over a PFP find it easier to control the self-injection process with a syringe.[25] Similarly patients who are not at ease with technology may choose the CZP PFP in preference to the e-Device.[18] These results highlight the importance of patient choice when selecting a self-injection device.

Limitations

The number of patients involved in this study was small (n=59). As a result, it may not be possible to generalise these results to other patient groups or populations. Additionally, patients opted into the study, which may lead to selection bias as patients willing to participate in a study testing new devices may be more open to alternative treatment delivery options. However, both this approach and the number of patients included are common for a pilot study.[26] Furthermore, the patients who participated in this study all had previous experience of self-injection, with the results of the pre-ASI questionnaire suggestive of considerable prior self-injection experience. This may further limit the generalisability of the results to the wider patient population, which includes individuals who are self-injection-naïve.

The e-Device was only used to self-inject three times over this study (although patients could choose to continue to use the e-Device once the study had ended). Furthermore, patients were not recruited based on any reported problems with their previous self-injection device. These factors could have biased the results in favour of patients' previous self-injection devices, due to more extensive experience and established device-specific self-injection routines that increase feelings of control over drug administration.[17] Indeed, as mentioned previously, research has suggested patients who prefer using a PFS over a PFP find it easier to control the self-injection process with a syringe.25 In addition, since patients were only followed for four weeks in this study, these results only apply to initial patient preference and satisfaction levels and cannot be generalised to longer timelines.

Finally, patients in Sweden did not answer all questions in the pre- and post-ASI questionnaires therefore it was not possible to include these patients in the ASI domain analyses. This reduced the number of patients who successfully completed the study. However, for questions that were answered by the Swedish cohort, results are consistent with those from Denmark and the Netherlands (Supplementary Figures S2–5) suggesting additional answers from Sweden would not change overall conclusions.

Conclusion

Patients perceived the e-Device as easy to use and handle, and were able to successfully administer self-injections. The e-Device was the preferred device for most patients, and the training materials were positively rated. This suggests access to an e-Device may help enhance patient experience, which could improve anti-TNF adherence and patient outcomes. The fact that some patients preferred their previous self-injection device demonstrates the importance of having a portfolio of devices available for patients to choose from, to ensure maximum satisfaction for all patients.

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Conflicts of Interest

BP & MP: No disclosures to declare. BvdB: Received grant/research support from: UCB Pharma, Pfizer, Abbvie; Speakers bureau: Pfizer, AbbVie, UCB Pharma, Biogen, Sandoz. Delivered consultancy work for UCB Pharma, Novartis and Pfizer. LEK: Received grant/research support from: UCB Pharma, Biogen, Janssen Pharmaceuticals, and Novartis; Speakers bureau: Pfizer, AbbVie, Amgen, UCB Pharma, BMS, Biogen, MSD, Novartis, Eli Lilly, and Janssen Pharmaceuticals. EvB, RB, IM, SW, HK & LB: Employee of UCB Pharma. TSJ: Received grant/research support from: AbbVie, Roche, Novartis, UCB Pharma, Biogen, Eli Lilly.

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Supplementary material S1. Questionnaires

Pre-ASI Questions

Domain: Feelings about self-injection (ranked from 0–4, where 0 is 'Not at all' and 4 is 'Extremely')

Q1. In general, how afraid are you of needles?
Q2. In general, how afraid are you of having an injection?
Q3. How anxious do you feel about giving yourself an injection?

Domain: Self-confidence (ranked from 0–4, where 0 is 'Not at all' and 4 is 'Extremely')

Q4. How confident are you about giving yourself an injection in the right way?
Q5. How confident are you about giving yourself an injection in a clean and sterile way?
Q6. How confident are you about giving yourself an injection safely?

Post-ASI Questions

Domain: (Negative) feelings about self-injection (ranked from 0–4, where 0 is 'Not at all' and 4 is 'Extremely')

Q1. In general, how afraid are you of needles?
Q2. In general, how afraid are you of having an injection?
Q3. How anxious do you feel about giving yourself an injection?

Domain: Self-image (ranked from 0–4, where 0 is 'Not at all' and 4 is 'Extremely')

Q4a. How self-conscious would you feel about using the ava® e-Device around your family?
Q4b. How self-conscious would you feel about using the ava® e-Device around your friends?
Q4c. How self-conscious would you feel about using the ava® e-Device around people you don't know?

Domain: Self-confidence (ranked from 0–4, where 0 is 'Not at all' and 4 is 'Extremely')

Q5a. How confident are you about giving yourself an injection in the right way?
Q5b. How confident are you about giving yourself an injection in a clean and sterile way?
Q5c. How confident are you about giving yourself an injection safely?

Domain: Pain and skin reactions (ranked from 0–4, where 0 is 'Not at all' and 4 is 'Extremely')

Q6a. During and/or after the injection, how bothered were you by pain?
Q6b. During and/or after the injection, how bothered were you by a burning sensation?
Q6c. During and/or after the injection, how bothered were you by a cold sensation?
Q6d. During and/or after the injection, how bothered were you by itching at the injection site?
Q6e. During and/or after the injection, how bothered were you by redness at the injection site?
Q6f. During and/or after the injection, how bothered were you by swelling at the injection site?
Q6g. During and/or after the injection, how bothered were you by bruising at the injection site?
Q6h. During and/or after the injection, how bothered were you by hardening at the injection site?
Q6i. During and/or after the injection, how bothered were you by bleeding from the injection site?
Q6j. During and/or after the injection, how bothered were you by medication leaking from the skin at the injection site?

Domain: Ease of use (ranked from 0–5, where 0 is 'Very difficult' and 5 is 'Very easy')

Q7a. How difficult or easy was it to read and follow the ava® e-Device instructions?
Q7b. How difficult or easy was it to learn how to use the ava® e-Device?
Q7c. How difficult or easy was it to remove the needle cap of the ava® e-Device?
Q7d. How difficult or easy was it to hold the ava® e-Device while preparing it and giving yourself medication?
Q7e. How difficult or easy was it to hold the ava® e-Device at the correct angle for the injection?
Q7f. How difficult or easy was it to depress the plunger or button on the ava® e-Device?
Q7g. How difficult or easy was it to administer the injection without any help?
Q7h. How difficult or easy was it to control the injection speed?
Q7i. How difficult or easy was it to pause when giving yourself an injection?
Q7j. How difficult of easy was it to stop with giving yourself an injection?
Q7k. How difficult or easy was it to be sure that the injection gave you the correct amount of medication?
Q7l. How difficult or easy was it to know when the injection is complete?
Q7m. How difficult or easy was it to remember when to take your next injection?
Q7n. How difficult or easy was it to store the ava® e-Device?
Q7o. How difficult or easy was it to travel with the ava® e-Device?
Q7p. How difficult or easy was it to use the ava® e-Device?
Q8. How does the device fit in your hand? (ranked from 0–4, where 0 is 'Very uncomfortably' and 4 is 'Very comfortably')

Domain: Satisfaction (ranked from 0–4, where 0 is 'Very dissatisfied' and 4 is 'Very satisfied')

Q9. How satisfied are you with the way the ava® e-Device delivers your medication?
Q10. After this study, how confident would you be to give yourself injections at home with the ava® e-Device? (ranked from 0–4, where 0 is 'Not at all' and 4 is 'Extremely')
Q11. How easy was it to give yourself an injection with the ava® e-Device? (ranked from 0–4, where 0 is 'Not at all' and 4 is 'Extremely')
Q12. How satisfied are you with your ability to control your injection (e.g. stop, pause, change speed) with the ava® e-Device?
Q13. How satisfied are you with the time it takes to inject the medication with the ava® e-Device?
Q14. Overall, how convenient is the ava® e-Device? (ranked from 0–4, where 0 is 'Very inconvenient' and 4 is 'Very convenient')
Q15. After this study would you choose to continue self-injecting your medication with the ava® e-Device? (ranked from 0–4, where 0 is 'Definitely not' and 4 is 'Definitely')
Q16. Overall, how satisfied are you with the ava® e-Device? (ranked from 0–4, where 0 is 'Very dissatisfied' and 4 is 'Very satisfied')

Preference Questionnaire

Each question asks the patient to choose between the e-Device, PFS, PFP or state they have no preference.

Q1. Which self-injection device do you prefer based on how safe the device is to use?
Q2. Which self-injection device do you prefer based on how confident you are when using the device?
Q3. Which self-injection device do you prefer based on how easy the device is to hold?

Q4. Which self-injection device do you prefer based on your ability to control your injection (for example, stop, pause, change speed)?
Q5. Which self-injection device do you prefer based on how easy the device is to store?
Q6. Which self-injection device do you prefer based on how easy it is to travel with the device?
Q7. Which self-injection device do you prefer based on the time needed to perform your injection?
Q8. Which self-injection device do you prefer based on how convenient the device is to use?
Q9. Overall, which self-injection device do you prefer?

Implementation Questionnaire

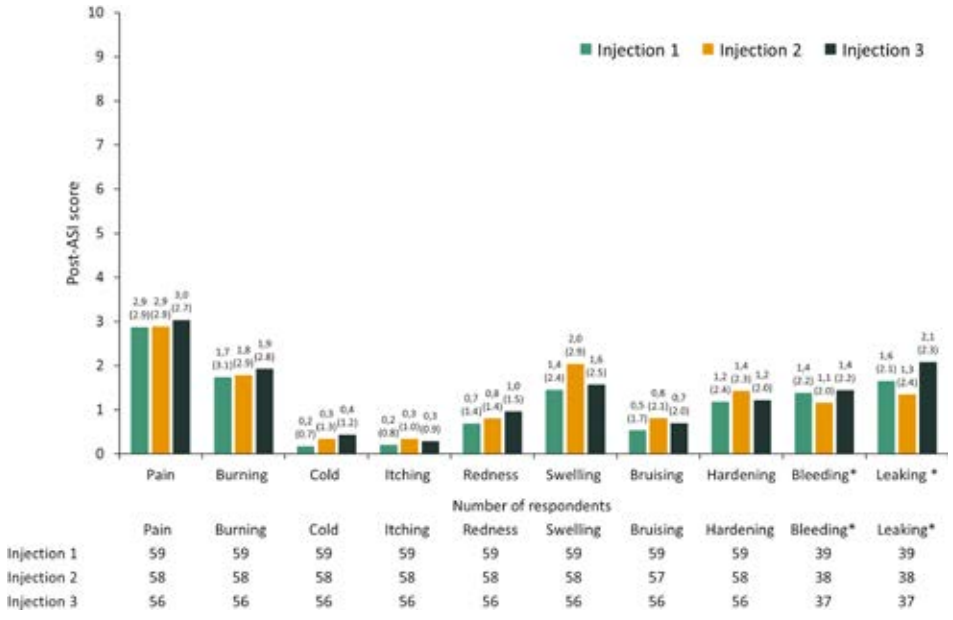
Ranked from 0–4, where 0 is 'Completely disagree' and 4 is 'Completely agree', patients can also choose 'Prefer not to say', unless specified otherwise.

Q1. The information in the training video was easy to understand.
Q2. There was enough information in the training video to teach me how to self-inject.
Q3. The training video was interesting to watch.
Q4. On a scale of 1 to 10 please rate how useful the training video was in training you to use the ava® e-Device. (Sliding scale: 1: Completely useless; 10: Completely useful)
Q5. Overall was there anything about the training video that you didn't like and would suggest could be changed? (Open ended question)
Q6. The information in the step-by-step guide was easy to understand.
Q7. There was enough information in the step-by-step guide to teach me how to self-inject.
Q8. The step-by-step guide was useful in helping me self-inject.
Q9. On a scale of 1 to 10 please rate how useful the step-by-step guide was in training you to use the ava® e-Device. (Sliding scale 1: Completely useless; 10: Completely useful)
Q10. Overall was there anything about the step-by-step guide that you didn't like and would suggest could be changed? (Open ended question)
Q11. What three things about the training materials did you find most helpful? (Open ended question)
Q12. Did you get all the information you needed from the training materials? (Choose 0: No; 1: Yes; 2: Not Sure; 3: Prefer not to say)
Q12b. If you did not receive all the information that you required from the training materials, what additional information would you have found useful? (Open ended question)

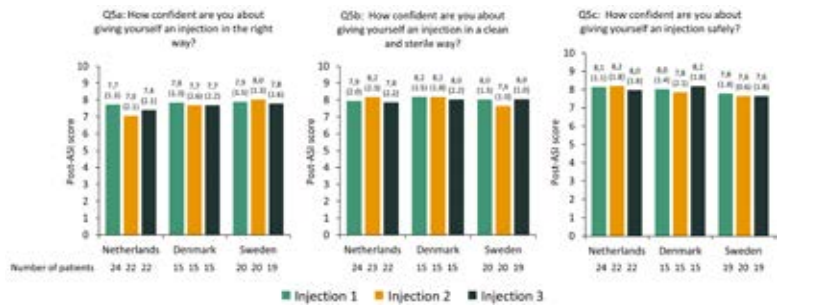
Supplementary Table 1. Implementation questionnaire results

Implementation Question (max. score 4)	Netherlands	Denmark	Sweden	Overall
	Score (n)			
Video				
Easy	3.9 (11)	3.9 (15)	3.6 (20)	3.8 (46)
Enough information	3.9 (11)	3.9 (15)	3.7 (20)	3.8 (46)
Interesting	3.1 (11)	2.8 (15)	3.1 (20)	3.0 (46)
Overall useful (max. 10)	8.4 (11)	7.9 (15)	8.8 (20)	8.4 (46)
Step-by-step guide				
Easy	3.7 (18)	3.7 (15)	3.6 (20)	3.7 (53)
Enough information	3.9 (18)	3.8 (15)	3.6 (20)	3.8 (53)
Useful	2.8 (18)	3.7 (15)	3.5 (20)	3.3 (53)
Overall useful (max. 10)	8.0 (18)	7.9 (15)	9.2 (20)	8.4 (53)

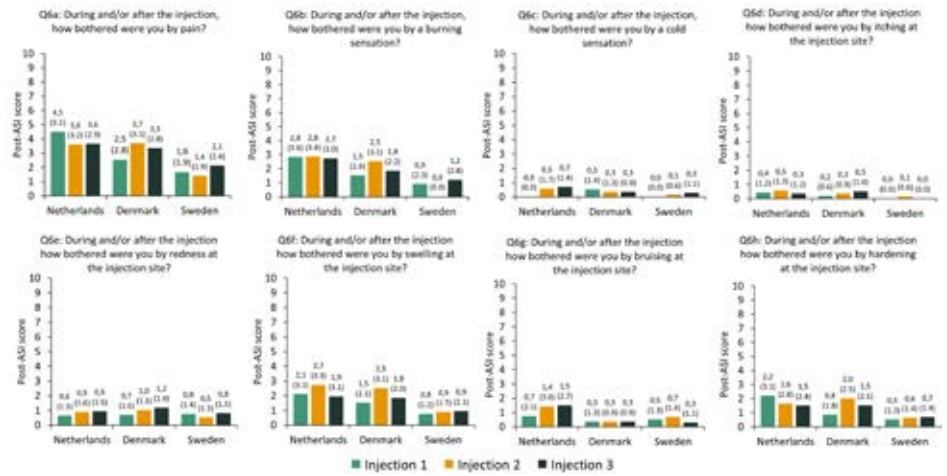
All questions are rated from 0–4, except where otherwise stated.



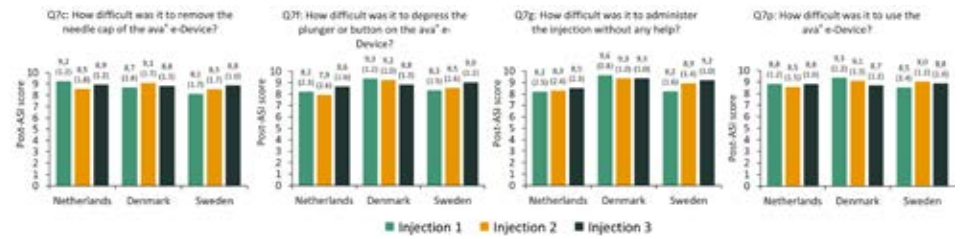
Supplementary Figure 1. Post-ASI pain and skin reaction domain: individual question results
*Patients from Sweden did not respond to questions referring to bleeding and leaking and, as a result, the number of respondents is lower for these questions. Data labels indicate mean (standard deviation). Item scores were converted to a 10-point scale (0: not at all; 10: extremely). ASI: assessment of self-injection.



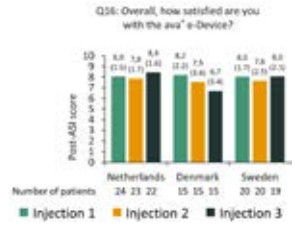
Supplementary Figure 2. Post-ASI self-confidence domain questions completed by all countries
Data labels indicate mean (standard deviation). Item scores were converted to a 10-point scale (0: not at all; 10: extremely).
ASI: assessment of self-injection.



Supplementary Figure 3. Post-ASI injectionsite reaction questions completed by all countries
Data labels indicate mean (standard deviation). Item scores were converted to a 10-point scale (0: not at all; 10: extremely).
ASI: assessment of self-injection.



Supplementary Figure 4. Post-ASI ease of use domain questions completed by all countries
Data labels indicate mean (standard deviation). Item scores were converted to a 10-point scale (0: not at all; 10: extremely).
ASI: assessment of self-injection.



Supplementary Figure 5. Post-ASI satisfaction domain question completed by all countries
Data labels indicate mean (standard deviation). Item scores were converted to a 10-point scale (0: not as all; 10: extremely).
ASI: assessment of self-injection.

Chapter 3

Tele-monitoring flares using a smartphone app in patients with gout or suspected gout – a feasibility study

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Abstract

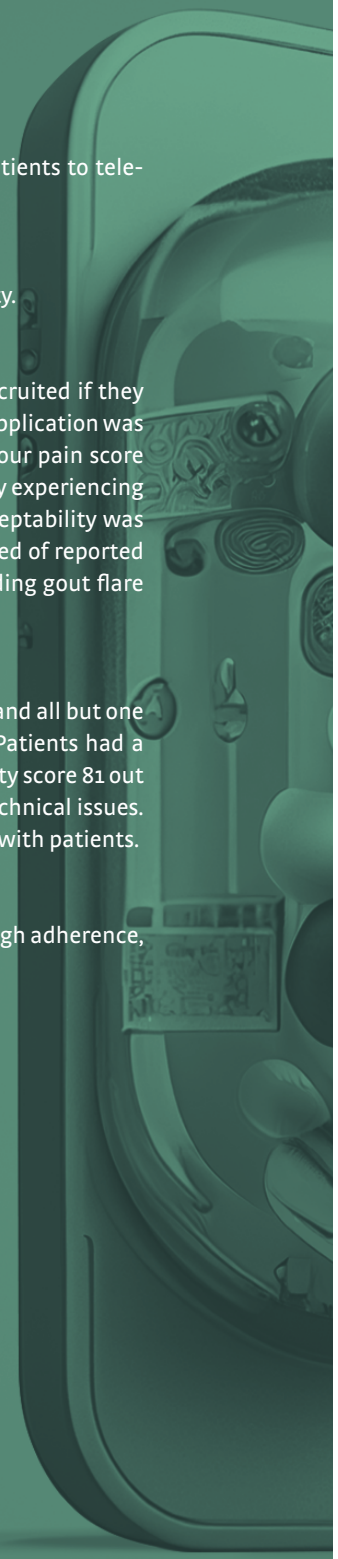
Background
Gout flares are painful and disabling. We developed a smartphone app for patients to tele-monitor gout flares surveyed by clinicians.

Objective
This study aimed to assess patient acceptability, technical and clinical feasibility.

Methods
Adult patients with either established gout or high suspicion thereof were recruited if they possessed a smartphone and reported a recent arthritis attack. A smartphone application was used to identify gout flares by asking during 90 consecutive days: 1) what is your pain score (0–10), 2) are your joints warm, 3) are your joints swollen and 4) are you currently experiencing a gout flare. The clinician was alerted via email if a flare occurred. Patient acceptability was assessed using the Technology Acceptance Model. Technical feasibility consisted of reported technical issues and clinical feasibility of actions taken by the clinician regarding gout flare alerts.

Results
29 included patients completed the study. Participants mean age was 57 years and all but one were male. Adherence rate was 96% (110 out of 2,910 queries were missed). Patients had a positive attitude towards app use, found the app very easy to use (mean usability score 81 out of 100) and were neutral to positive on its usefulness. There were four minor technical issues. A total of 100 gout flare alerts were generated that led to 18 proactive contacts with patients.

Conclusion
A smartphone app to monitor gout flares was developed and tested, showing high adherence, good acceptability and clinical feasibility for established gout patients.



Introduction

Patients with gout, one of the most frequent inflammatory arthritic diseases, may experience recurrent flares which are intensely painful and disabling in case of uncontrolled disease.[1] Recurrent and chronic inflammation in gout impairs quality of life.[2] As a result patients care most about frequency and intensity of flares when considering treatment efficacy over time.[3] Besides gout severity is, independent of hyperuricemia, associated with cardiovascular disease risk.[4,5] Hence frequency of gout flares is an important clinical gout outcome. For optimal gout management timely identification of flares and initiation of pharmacological treatment is needed according to European guidelines.[6] However patients often flare at home, without the clinician knowing, which limits timely and accurately monitoring of gout flares.

Ideally flares are identified at onset by patients and reported to the clinician to allow for fast and accurate diagnosis and early pharmacological treatment to subdue pain and increase daily functioning of the patient. Recently Gaffo et al validated a patient reported gout flare definition.[7] This flare definition was incorporated into a smartphone app to tele-monitor gout flares at home during clinical trials.[8] This study showed it was feasible to capture gout flares at onset using the app and was deemed very convenient by patients. Yet, tele-monitoring gout flares has not been applied to routine clinical practice.

Incorporation of the gout flare definition into a smartphone application may have several advantages for clinical care. It facilitates standardised monitoring between visits, giving insight to both patients and treating physicians in gout flare frequency and duration. One can act upon reported outcomes immediately or at later scheduled visits. Studies in rheumatoid arthritis have shown that implementing standardised monitoring improves both disease monitoring and clinical outcome when combined with protocolised treat-to-target therapy.[9]
To study the possibility of using a smartphone application to monitor gout flares between outpatient visits in patients with uncontrolled or suspected gout, we incorporated the patient reported flare definition in a smartphone query app. Monitoring reports were sent to a clinician's dashboard for surveillance and to allow timely provision of appropriate treatment strategies. To ascertain that gout flares can be detected using this smartphone app for the use in routine gout care, insight is needed into patient's opinions on its use and its burden in daily practice. This study aimed primarily to assess patient acceptability and technical feasibility of a smartphone app for tele-monitoring gout flares. Secondary outcome was to explore the clinical feasibility of the app and the possibility to act upon reported flares.

Methods

Study design and setting

This intervention study was conducted during 2018 and 2019 at the Sint Maartenskliniek in Nijmegen, the Netherlands. The study was approved by the ethics committee Arnhem – Nijmegen under registration number NL65917.091.18 and registered in the Dutch Trial Register as NL643510.

Participants

Adult patients visiting the rheumatologist with established gout or a high clinical suspicion of gout were invited to participate until thirty patients gave written informed consent. Patients were considered to have established gout if crystals were confirmed on microscopy analysis, tophi were present or if the patient fulfilled the ACR (American College of Rheumatology)/ EULAR (European League Against Rheumatism) criteria.[11] Patients with an unclassified arthritis in the last three months and suspicion of gout, as regarded by the rheumatologist, could be enrolled as patients with high clinical suspicion. Furthermore, patients were eligible for participation if they had at least had one self-reported arthritis attack in the past three months, possessed an Android or iOS-based smartphone and were able to communicate in Dutch.

Intervention

A smartphone application for queries (Q1.6) was used to incorporate elements of the patient reported gout flare definition by Gaffo[7] (see Supplementary Figure S1 for screenshots). The definition gout flare is met if three out of the following four questions score positive:

1) What is your current pain score on a zero to ten level? (positive if 4 or above)
2) Do you have warm joints?
3) Do you have swollen joints?
4) Are you currently experiencing a gout flare?

The tele-monitoring process is depicted in Figure 1. Patients installed the app which was programmed to query the user on a daily basis for 90 consecutive days. To optimise user-friendliness, questions were asked in the Dutch language and the regression tree definition as defined by Gaffo was applied.[12] This means that the first question was a screening question where scoring pain below 4 (indicating minimal pain) terminated the query, otherwise the patient had to answer the remaining questions. In the pilot phase patients could not view their responses. Encoded responses were transmitted real-time to a hospital dashboard that could be accessed by the research team consisting of two rheumatologists and one pharmacist. This dashboard showed a list of all patients, whether questions for that day were answered and whether the flare criterion was met. The dashboard opened up to the patient's overview. The research team received an email alert once daily if the patient reported definition was met (see Measurements: exploring feasibility for definitions) to enable the research team to provide the necessary care quickly.

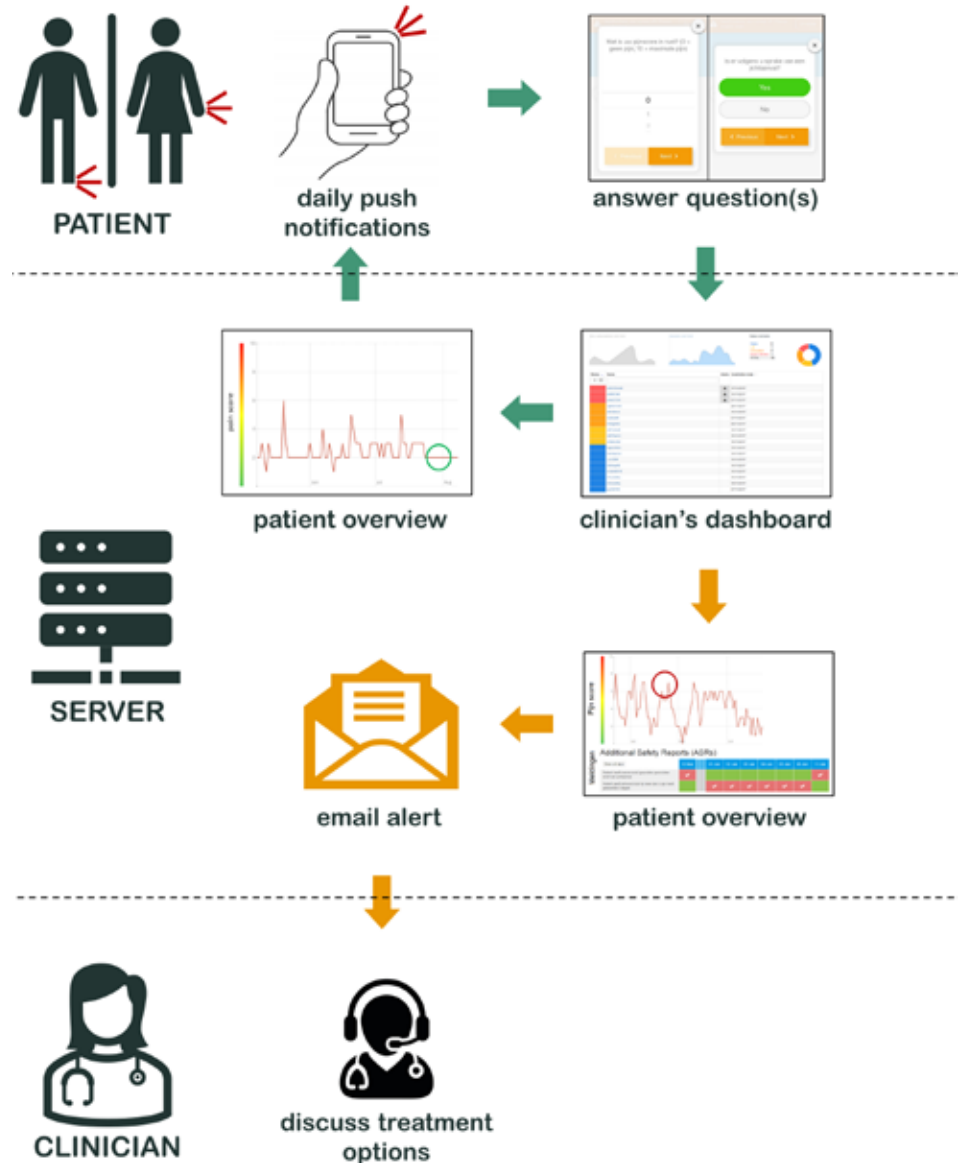


Figure 1. Tele-monitoring process from patient to server to clinician

Measurements: patient acceptability

Patient acceptability was assessed using the Technology Acceptance Model (TAM). The model postulates that actual use of a new technology is a result of the behavioural intention to do so. In turn, behavioural intention is jointly determined by the attitude towards using and perceived usefulness. Both determinants are influenced by the ease of use.[13] In figure 2 the Technology Acceptance Model is depicted together with the outcomes used in this study to measure the determinants of the model.

Actual use was measured using attrition rate and adherence rate to daily queries.
Attitude toward using was assessed using four questions of the user version of the Mobile Application Rating Scale (uMARS).[14] The questions of the uMARS that captured the overall feeling of the app and its potential use were selected by BP and BVDB. All other questions were omitted as they related to other aspects of mobile applications and even overlapped with ease of use and usefulness.
Perceived ease of use was scored using the Dutch version of the System Usability Scale (SUS)[15]. The SUS consists of ten statements scored on a 5-point Likert scale (totally agree – totally disagree). Taken together the SUS items yield a single score representing a composite measure of the overall usability. Bangor et al added an adjective scale to the SUS score ranging from worst (0 - 25) to best imaginable (90 – 100).[16,17]
Perceived usefulness was assessed with the perceived usefulness questionnaire by Davis[13] which was translated and adjusted to fit the purpose of the gout query app. This resulted in ten usefulness statements on a 5-point Likert scale (totally agree – totally disagree).
See Supplementary Data S2 for the complete questionnaire.

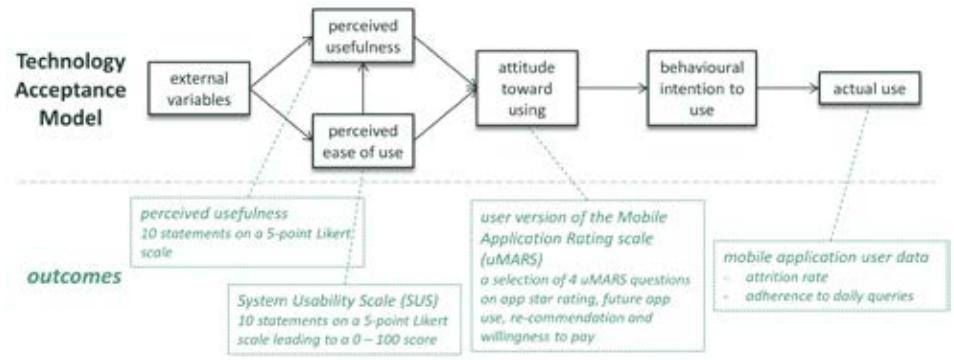


Figure 2. Technology Acceptance Model and the outcomes of this study

Measurements: exploring feasibility

Feasibility is the assessment of the practicality of, in this particular case, a healthcare innovation. There are many domains that can be assessed among which are technical, operational, clinical, resource and financial feasibility. As the patient is the one who should benefit most from the current innovation we chose to explore the feasibility of two domains: technical and clinical.

Technical feasibility was assessed by collecting all technical issues. These issues were either directly reported by patients or noted by the researcher when checking whether inactivity was due to technical issues.

Clinical feasibility was stratified for suspected and established gout patients because clinical follow-up differed. All patients received standard care according to the care protocols of the Sint Maartenskliniek. Patients with a suspicion of gout are instructed to phone the clinic when flaring to make an appointment for a visit to the clinic within 48 hours to try and obtain joint fluid for uric crystal detection. Patients with established gout are instructed to start anti-inflammatory therapy at the onset of flare symptoms (or increase in case of anti-inflammatory prophylaxis) and to call if a flare persists despite adequate treatment. When the clinician received an email alert from the tele-monitoring system, he decoded the patient research ID and looked into the patient's status. Patients with a high suspicion of gout were contacted the day the email alert was received. This allowed the clinician to invite the patient to the clinic within 48 hours to establish gout diagnosis. Patients with established gout were contacted only if the flare lasted beyond three days, as a flare lasting beyond three days despite treatment was defined an inadequate treated gout flare for the purpose of this study. During the call the clinician inquired on flare severity and evaluated treatment strategy. To have a general idea of how alerts of the app related to provided care, clinical feasibility was expressed with process parameters like the number of alerts generated, number of (timely) clinician-patient contacts and actions taken by the clinician. Because provided care could differ between patients, no end-of-prompt was set for generated alerts. Therefore one flare could generate multiple alerts and alert generation could continue even after the patient was consulted.

Sample size

In this feasibility study, we based our sample size on earlier publications of Kieser and Wassmer (1996) and Julious (2005) showing that a pilot sample of 20 to 40 with at least 12 patients per sample suffices.[18,19] As a consequence, the sample size was set at 30 patients to ensure the minimal of 12 patients with established and 12 with suspicion of gout.

Statistical analysis

Analysis was performed using descriptive statistics. Continuous variables were described using mean and standard deviation (SD) or, in case of non-nominal distributed data, median and interquartile range (IQR). Categorical variables were expressed as percentages. All data were analysed using STATA version 13.1.

Results

Participants

Thirty patients gave consent but one patient was excluded as he received the diagnosis rheumatoid arthritis before starting the study. Participants had a mean age of 57 years [SD ± 13] and almost all (97%) were male (see Table 1). Seventeen patients had a diagnosis of established gout (disease duration after diagnosis 3.5 months [IQR 2.4 – 14.1]) of which 16 patients (94%) used urate lowering therapy. Twelve patients with a suspicion of gout participated of which four (33%) used urate lowering therapy and all used anti-inflammatory drugs.

Patient acceptability

Actual use

Attrition rate was 0% as no patient prematurely quit. Overall adherence to queries was 96% as 110 out of 2,710 queries were missed. Three patients were responsible for 60% of the missing queries (n=66) where 16 patients never missed a query.

Attitude toward using

Median overall rating of the app was 4 out of 5 stars [IQR 4 – 5]. Fifteen patients (52%) would use the app daily. Twenty-four patients (48%) would recommend the app to others. Eleven patients (38%) would consider paying for the app.

Perceived ease of use

Mean SUS score was 81 ± 8 and 27 (93%) patients rated usability good to excellent.

Perceived usefulness

Overall, patients perceived the usefulness of the app as neutral to slightly positive (see figure 3). The statement 'I like the fact that the doctor can immediately see when I'm in pain' scored best (IQR 4 – 5).

Table 1. Characteristics of study participants[a]

Characteristic	All (n = 29)	Established gout (n = 17)	Suspicion of gout (n = 12)
Age in years, mean (SD)	57 (13)	59 (14)	54 (13)
Male sex, n (%)	28 (97)	17 (100)	11 (92)
Established gout, n (%)		17 (100)	
Time since diagnosis in months[b], median [IQR]		3.5 [2.4 – 14.1]	
Crystal proven, n (%)		9 (53)[c]	
Tophi's present, n (%)		7 (42)[c]	
Flares in the previous 3 months[d], n (%)			
1	26 (90)	16 (94)	10 (83)
2	2 (7)	-	2 (17)
3 or more	1 (3)	1 (6)	-
Use of urate lowering therapy, n (%)	20 (69)	16 (94)	4 (33)
Allopurinol	16 (80)	13 (81)	3 (75)
Benzbromaron	3 (15)	2 (13)	1 (25)
Febuxostat	1 (5)	1 (6)	-
Use of anti-inflammatory drugs, n (%)	29 (100)	17 (100)	12 (100)
Colchicine, cont. n (%)/proph. n (%)	18 (62) / 7 (24)	13 (76) / 2 (12)	5 (42) / 5 (42)
Prednisone, cont. n (%)/proph. n (%)	2 (7) / 5 (17)	1 (6) / 3 (18)	1 (8) / 2 (17)
NSAID's, cont. n (%)/proph. n (%)	6 (21) / 11 (38)	3 (18) / 7 (41)	3 (25) / 4 (33)
Coxib's, cont. n (%)/proph. n (%)	1 (3) / -	1 (6) / -	-
Urate level in mg/ml, mean (SD)	0.39 (0.11)	0.36 (0.10)	0.42 (0.11)
CKD-EPI in ml/min, mean (SD)	85 (16)	84 (27)	86 (14)

[a] Abbreviations: SD = standard deviation; IQR = interquartile range; cont. = continuous use; proph. = prophylactic or use in case of a flare; NSAID's = non-steroidal anti-inflammatory drugs; Coxib's: selective cyclo-oxygenase-2 inhibitor; CKD-EPI = glomerular filtration rate estimate from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration formula [b] As confirmed by the rheumatologist [c] Four patients had neither crystal proven gout nor tophi's present but did fulfil the ACR/EULAR criteria for gout. [d] Self-report by patients as documented by the rheumatologist

Exploring feasibility

Regarding technical feasibility: four technical issues were reported during the study. Two patients had trouble installing the application and two issues involved a temporarily disruption of the queries and led to 13 missed queries. All issues were considered minor and resolved by the research team.

Eleven of the 17 patients (65%) with established gout experienced a total of 20 flares during the three-month period. Median flare duration was 1.5 days (range 1 to 8 days). Five flares lasted beyond 3 days, generating an alert, of which one flare was discussed during an already planned consultation. The remaining four alerts were followed up with a phone call within four days of symptom onset. No action was deemed necessary for three patients whereas one patient was invited to the clinic the next day where an intra-articular injection was placed and medication adjusted.

In the 12 suspected gout patients seven patients (58%) generated 95 alerts out of 630 queries (15%) with three patients responsible for 79 alerts (83%). Conform protocol, 14 patient contacts with the clinician followed, of which 7 (50%) were within 48 hours (weekends excluded). These contacts led to two alternative diagnoses (one rheumatoid arthritis and one psoriatic arthritis), four medications being started, one medication adjustment and three emergency visits to the clinic where one intra-articular injection was placed and one diagnostic screening performed. During follow-up the following clinical problems were encountered that led to repeated alert generation: non-adherence to gout flare therapy, alternative diagnoses and comorbidity (osteoarthritis).

Figure 3. Results of the perceived usefulness statements
A dot represents the median and a line the interquartile range.

Discussion

This feasibility study aimed to assess the patient acceptability and feasibility of tele-monitoring gout flares using a smartphone app as part of routine gout care. The app was used continuously with few minor technical issues. Patients had a positive attitude towards app use, found the app easy to use and were neutral to positive on its usefulness. Clinically, it was feasible to timely contact all patients with established gout but not actionable to contact patients with suspicion of gout at each alert.

Patient acceptability

The adherence found in this study is very high compared to that reported in similar literature.[20] Possibly the high adherence is a result of the easy and short patient definition as Elmagboul et al., who used the same definition, showed similar adherence rates when monitoring gout flares on a weekly basis for six months using a smartphone app and interactive voice response.[8] Additionally, in a qualitative study patients stressed that flare monitoring should be included in a gout self-management app.[21] These results comply with the theory of the Technology Acceptance Model that high app use is a result of high usability and usefulness that was also found in our study.

High adherence could also have been the result of selection bias, as patients participated after invitation by their rheumatologist and no record was held of patients who were not eligible or who declined invitation. Included participants were relatively young and it has been shown that a younger age leads to higher eHealth adherence so possibly we selected the early adopters.[20] Adherence rates in clinical practice can be lower especially when tele-monitoring exceeds our three month study period. Colls et al. found adherence rates to be highest in the first month and then a decline over a period of 6 months.[20] The use of a short low-key screening question (pain-score) instead of the full questionnaire can be an important factor in maintaining high adherence over time in the present study. Fortunately, lower adherence rates could still suffice for the purpose of catching flares because patients do not flare on a daily basis.

Technical and clinical feasibility

Our findings demonstrated technical and clinical feasibility of the gout app. Few technical issues were encountered and these were easy to resolve.

At the clinical level, the app functioned as expected in monitoring occurrence and duration of gout flares. However regarding alert generation several issues were identified, especially in translating alerts into clinical action. One flare was able to generate multiple alerts as we did not build an end-of-prompt definition in the alert algorithm. Therefore alerts did not terminate upon action, which can be built in as future improvement.

Furthermore we included suspected gout patients to increase generalisability by encompassing the full range of patients who are seen during routine clinical practice, even though the flare definition is not validated for patients with a suspicion of gout. In retrospect, this group may not be suitable for using the gout flare criterion on a daily basis as alternative diagnoses may lead to repeated alerts in case of a more chronic form of arthritis. In patients with established gout the app alerts functioned as a valuable monitoring tool. However, the additional value of pro-active contact was considered low as only one of five alerts the patient was invited to the clinic for consultation and intra-articular injection. In further research the query frequency could be optimised by using an algorithm that lowers query frequency when flares subside, especially with longer use of the app.

Clinical implications

This study shows high patient adherence to tele-monitoring symptoms using a smartphone app. In clinical practice tele-monitoring of gout flares would provide a real-time between-visits overview of the frequency and duration of gout flares in patients with uncontrolled gout. The use of a standardised gout flare patient-reported outcome makes comparison between patients and within population mean an insightful possibility for both clinicians and patients. Furthermore, anonymised tele-monitoring data combined with clinical outcomes gives valuable insight in gout flare prognostics and treatment options. There is a case for acting upon flares in patients with a suspicion of gout but in patients with established gout the additional value of a pro-active intervention remains to be seen.

Future work

As this is a feasibility study there are steps to take before fully implementing tele-monitoring of gout flares in clinical practice. Firstly, acceptability from the clinician's perspective should be assessed because participation of all concerned parties is crucial for implementation. Even more so because clinicians should guarantee continuous monitoring of the dashboard and take appropriate clinical actions. Secondly, the app's value as a diagnostic tele-monitoring tool for facilitating routine gout care could be increased. In its current form the app is most useful for established gout patients with active disease and we do not advice use of the app in patients with a suspicion of gout. Adjustment and validation of apps like this one may result in a more useful eHealth tool in this patient group.[22] Lastly, the effectiveness of tele-monitoring gout flares should be evaluated on clinical outcomes like Day et al.[23] Such a study will provide a better estimate of patient acceptability as inclusion will extend beyond the early adopters.

Conclusion

Taken together, a smartphone app to telemonitor gout flares was developed and tested. Telemonitoring was technically feasible, had high adherence and good patient acceptability. Clinically, our application made it feasible to act on flares as they occur in established gout patients during this study. The current patient reported definition for gout flares is not suitable for patients with a suspicion of gout.

Acknowledgements

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Conflicts of Interest

All authors declare no conflict of interest.

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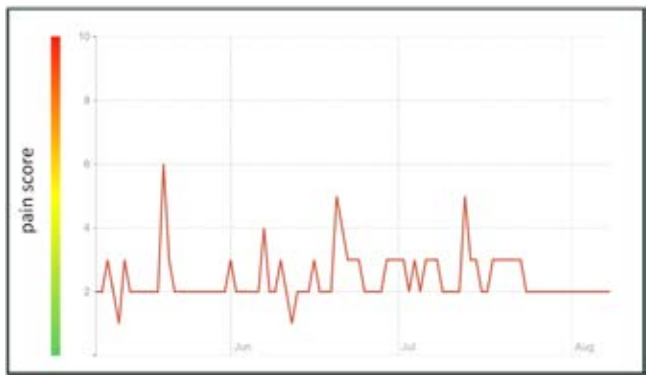
Supplementary material S1. Screenshots of the gout app and its dashboard

Supplementary Figure 1. Screenshot of the smartphone application
The screen on the left is the first screener question and reads 'What is your pain score when in rest? (0 = no pain; 10 = maximum pain). The screen on the right is the final question (only shows when pain is scored 4 or above) and reads 'do you think you are experiencing a gout flare?'.



Supplementary Figure 2. Screenshot of the clinician's dashboard
The dashboard shows the patient's pain score over time. Additionally, the clinician has insight in the answer of the three remaining criteria (information not shown).

Supplementary material S2. Questionnaires

Part 1: perceived ease of use (SUS)

Ranked from 0–4, where 0 is 'Totally disagree' and 4 is 'Totally agree'.

1. I think that I would like to use the gout app frequently.
2. I found the app unnecessarily complex.
3. I thought the app was easy to use.
4. I think that I would need technical support to be able to use the app.
5. I found the various functions in the app well integrated.
6. I thought there was too much inconsistency in this app.
7. I imagine that most people would learn to use this app very quickly.
8. I found the app very cumbersome to use.
9. I felt very confident using the app.
10. I needed to learn a lot of things before I could get going with this app.

11. Have you had problems using or installing the app?
- ☐ Yes, namely .....
- ☐ No

12. Does the app allow you to customise the settings and preferences that you would like to (e.g. notifications)?
- ☐ Allows complete tailoring of preferences and remembers all settings.
- ☐ Allows numerous options for customisation.
- ☐ Basic customisation to function adequately.
- ☐ Allows little customisation and that limits app's functions.
- ☐ Does not allow any customisation or requires setting to be input every time.

13. Is the app interactive?
- ☐ The app is fully interactive and responds to my input.
- ☐ Offers a variety of interactive features and user input options.
- ☐ Basic interactive features to function adequately.
- ☐ Some interaction, but not enough which limits app's functions.
- ☐ No interactive features and/or no response to user input.

14. How accurately and fast does the app function?
- ☐ The app functions perfectly.
- ☐ The app functions well with some minor negligible problems.
- ☐ The app functions overall but some technical issues need fixing.
- ☐ Some functions work but the rest needs urgent fixing.
- ☐ The app is broken/crashes continuously.

15. What do you think of the visual design of the app?
- ☐ Professional, simple, clear and logically organised.
- ☐ Mostly clear, able to locate, read and select everything.
- ☐ Satisfactory, few problems with locating, reading or selecting items.
- ☐ Bad design, hard to locate, read or select items.
- ☐ Very bad design, impossible to locate, read or select (part of the) items.

16. How high is the quality/resolution of the graphics?
- ☐ Very high quality/resolution graphics – proportionate and consistent.
- ☐ High quality/resolution graphics – mostly proportionate and consistent.
- ☐ Moderate quality graphics, not always consistent.
- ☐ Low quality, disproportionate and inconsistent.
- ☐ Graphics appear amateur – very poor quality and design.

17. How good does the app look?
- ☐ Very attractive
- ☐ Somewhat attractive
- ☐ OK – attractive nor unattractive
- ☐ Fairly unattractive
- ☐ Very unattractive

18. What is your overall (star) rating of the app?
- ☐ Five stars
- ☐ Four stars
- ☐ Three stars
- ☐ Two stars
- ☐ One star

Part 2: perceived usefulness of the gout app (adapted from Davis Jr & uMARS).

Ranked from 0–4, where 0 is 'Totally disagree' and 4 is 'Totally agree'.

19. Using the app leads me to have faster contact with the doctor about a flare.
20. Using the app helps me to cope with gout.
21. Using the app makes me take medication earlier during a flare.
22. I think that through using the app my gout improved.
23. Using the app supports me with the gout symptoms I experience.
24. I like the idea that the doctor can directly see if I am in pain.
25. I found the phone call from the Sint Maartenskliniek useful.
26. The app makes me spend more time on gout.
27. Do you regard this as positive?
- ☐ Yes, because .....
- ☐ No, because .....

28. Using the app has changed my attitude towards gout flares.
29. Using the app makes me reach out for help during a gout flare.
30. The app has changed my behaviour concerning gout flares.

31. Is the app content appropriate for the target audience?
- ☐ Designed specifically for the target audience, no issues found
- ☐ Designed for the target audience, with minor issues
- ☐ Acceptable but inappropriate/confusing/unclear at times.
- ☐ Mostly inappropriate, unclear or confusing.
- ☐ Completely inappropriate, unclear or confusing.

32. Would you recommend this app to other people with gout?
- ☐ Definitely – I would recommend this app to everyone with gout.
- ☐ Probably – there are many people with gout I would recommend this app to.
- ☐ Maybe – there are several people with gout I would recommend this app to.
- ☐ Unlikely – there are very few people I would recommend this app to.
- ☐ Not at all – I would not recommend this app to anyone with gout.

33. Have you ever skipped a question in the past 90 days?
- ☐ Yes, because .....
- ☐ No

34. How many times do you think you would use this app in the next 12 months?
- ☐ Multiple times a day.
- ☐ Once a day.
- ☐ Once to several times a week.
- ☐ Once to several times a month.
- ☐ Once to several times a year.
- ☐ Not at all.

35. Would you pay for this app?
- ☐ Most certainly.
- ☐ Probably.
- ☐ Maybe.
- ☐ Probably not.
- ☐ Most certainly not.

Part 3: additional questions

36. Do you have any comments or recommendations that you would like to inform the researchers about?
- ☐ Yes, namely .....
- ☐ No

37. Can we reach out to you for further research?
- ☐ Yes
- ☐ No

Chapter 4

Effect of eHealth interventions on improving medication adherence in adults with long-term medication – a systematic review

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Abstract

Background
Medication nonadherence leads to suboptimal treatment outcomes making it a major priority in healthcare. eHealth provides an opportunity to offer medication adherence interventions with minimal effort from healthcare providers whose time and resources are limited.

Objective
The aim of this systematic review is twofold: 1) to evaluate effectiveness of recently developed and tested eHealth interventions on medication adherence in adult patients using long-term medication, 2) to describe strategies among effective interventions.

Methods
MEDLINE, EMBASE, Cochrane Library, PsycINFO and Web of Science were systematically searched from January 2014 to July 2019 as well as reference lists and citations of the identified articles. Eligible studies fulfilled the following inclusion criteria: (1) randomised controlled trial with a usual care control group; (2) applying an interactive eHealth intervention aimed at the patient or patient's caregiver; (3) medication adherence as primary outcome irrespective of follow-up period; (4) with a total sample of at least 50 adult patients using long-term medication. Methodologic quality was assessed using the Cochrane risk of bias tool. Selection and quality assessment of studies was performed by two researchers independently. A best-evidence synthesis was performed.

Results
Of the 9,046 records screened, 23 randomised clinical trials were included reporting on 29 interventions. A majority, 17 out of 29 interactive interventions, had a significant positive effect on medication adherence. Our best evidence synthesis provided strong evidence for a positive effect of interventions using SMS and/or interactive voice response, mobile applications and calls as mode of providing adherence feedback. Intervention strategies to teach medication management skills, to improve health care quality by coordinating medication adherence care between professionals and to facilitate communication and/or decision making between patients and healthcare providers also showed strong evidence for a positive effect.

Conclusion
Overall, this review supports the hypothesis that interactive eHealth interventions can be effective in improving medication adherence. Interventions that support behaviour change by improving patient's treatment involvement and medication management skills are most promising and should be considered for implementation in practice.

Introduction

Long-term medication aims to reduce the risk of disease progression, comorbidity and mortality.[1] These outcomes will only be reached when patients adhere to their medication. Presumably 50% of all patients with long-term medication are nonadherent, leading to suboptimal treatment outcomes.[2,3] Medication adherence is defined as the extent to which medication taking behaviour corresponds with the medication regimen agreed upon with the healthcare professional.[4] Medication-taking behaviour is multifaceted as this behaviour is influenced by different factors such as experience, beliefs and culture. What is more, medication-taking behaviour can differ between each drug and may change over time. Targeted, timely interventions enhancing medication adherence have therefore become one of the major priorities in healthcare. Despite efforts, randomised controlled trials assessing medication adherence-enhancing interventions have demonstrated limited effectiveness.[5–9] Besides, when effective the interventions did not reveal similar intervention strategies because interventions differed markedly.[3,5–7]

eHealth might provide an opportunity to offer accessible, interactive, timely and feasible medication adherence interventions that require minimal effort from healthcare providers whose time and resources are limited. eHealth or telemedicine - these words are used interchangeably - is defined as the use of information and communication technology in healthcare.[10] These technologies can facilitate tailored and interactive solutions like targeted education, consistent support and skill acquisition. Additionally, there is the possibility to toggle between modalities and formats to suit different behaviour, learning styles, preferences and literacy levels.[11] Thus, the multi-faceted and versatile medication-taking behaviour can well be targeted by eHealth interventions.

eHealth seems a promising way forward but recent systematic reviews on the effectiveness of eHealth interventions in improving medication adherence showed conflicting results.[12–15] These latter reviews focused on one specific long-term condition and have led to fragmented knowledge on the effectiveness and strategies of eHealth interventions. Medication nonadherence is a challenge across all long-term conditions; evidence on eHealth interventions should therefore be clustered to comprehensively investigate effectiveness of these eHealth interventions and facilitate generalisability of study findings. Linn et al (2011) and Sieben et al (2014) found promising results across long-term conditions but the fast developments in eHealth render those results outdated.[5,16] Additionally, their included studies had methodological limitations and their definition of eHealth as 'internet' was too narrow. Therefore the aim of our systematic review is twofold: 1) to evaluate effectiveness of recent eHealth interventions on medication adherence in adult patients using long-term medication, 2) to describe applied strategies within effective interventions.

Methods

This systematic review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement[17] and was completed according to the registered protocol PROSPERO 2019 CRD42019088873.

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Search strategy & study selection

Searches were undertaken in MEDLINE, EMBASE, Cochrane Library, PsycINFO and Web of Science to identify eligible studies. The search strategy comprised three blocks: eHealth, medication adherence and randomised clinical trial (see Supplementary Material S1 for the MEDLINE search strategy). Reference lists and citations of included studies were checked to ensure literature saturation. Titles and abstracts were screened and full text articles assessed by two researchers (BP and BvdB or JV) independently. Discrepancies between researchers were resolved through discussion or by reaching consensus with a third researcher.

Eligibility criteria

Eligible studies fulfilled the following inclusion criteria: (1) randomised controlled trial with a usual care control group; (2) applying an interactive eHealth intervention aimed at the patient or patient's caregiver; (3) medication adherence as primary outcome irrespective of follow-up period; (4) with a total sample of at least 50 adult patients using long-term medication as determined by Zwikker et al. 2014[18] ; (5) published between 2014 and July 2019. Only peer-reviewed English full text articles were included. We considered all interventions solely applied over distance as eHealth interventions (e.g., online portals, telephone calls). Blended care interventions, where face-to-face contact is combined with online components, were excluded. More specifically, we only included interactive eHealth interventions because medication-taking behaviour is multifaceted and interaction increases chances of changing nonadherent behaviour. Interventions were considered interactive if there was tele-feedback regardless by whom on medication adherence (e.g., bi-directional text messaging, sending adherence reports). Only validated medication adherence outcomes (i.e., objective measures or subjective measures that have been compared to objective measures) were taken into account.

Quality of evidence

Two researchers (BP and JV) independently assessed the internal validity of included studies using the Cochrane Collaboration's tool for assessing risk of bias.[19] Seven domains were scored low (+), high (-) or unclear (?) risk of bias. Because blinding of participants and personnel is hardly feasible in studies evaluating interventions aimed at adherence this domain was considered high risk (-) for all studies. Studies with a positive score (+) on at least five domains were considered high quality studies. If relevant information was not reported, the corresponding author was contacted to request additional information.

Data extraction

A standardised template was made to extract data on study characteristics, eHealth interventions and medication adherence outcomes. Details of the eHealth interventions were extracted according to the Template for Intervention Description and Replication (TIDieR) checklist.[20] Additionally, the mode of adherence feedback of each eHealth intervention was extracted. We distinguished the following modes of adherence feedback: monitoring device, short text messaging (SMS), interactive voice response (IVR), mobile application, call or e-training. Intervention strategies were categorised based on the strategies defined by Löwe et al: to support behaviour change; to inform and educate; to support; to teach skills; to minimise risk and harms; to facilitate communication and/or decision making and to improve health care quality.[21] Only the primary adherence outcome at study endpoint was extracted, secondary adherence measures or multiple time points were disregarded. For continuous outcomes Cohen's D for assessing effect size was calculated if means and standard deviations were provided.[22] Dichotomous outcomes were recalculated to odds ratio's (OR). Additionally, if the authors reported a statistical significance favouring the intervention group compared to the control group this was scored positive (+). A negative score (-) means there was no statistically significant difference to report. Data were extracted by one researcher (BP) and checked for accuracy by a second researcher (JV).

Data analysis

Statistical data pooling was not feasible due to heterogeneity between studies and interventions. Therefore a best evidence synthesis was performed to examine the effectiveness of eHealth interventions on medication adherence. The Cochrane Back Review Group defines four levels of evidence: strong, moderate, limited and conflicting evidence.[23] Strong evidence reflects consistent (i.e. 75 percent or more of the studies report results in the same direction) results among two or more high quality studies. Moderate evidence reflects consistent results of one high quality study and two or more lower quality studies. Limited evidence reflects the result of one lower quality study. Conflicting evidence reflects inconsistent results among two or more studies. If there were two or more high quality studies, the lower quality studies were disregarded in the best evidence synthesis. A post-hoc sensitivity analysis was performed to examine the robustness of the best evidence synthesis using a different cut-off score for the risk of bias of the studies.

Results

Search results

Figure 1 shows a flow diagram of the literature search which provided a total of 9,046 publications for screening and yielded 22 articles reporting on 29 interactive eHealth interventions.[24–43] One article, by Reese et al. (2017) reported on two studies.[32] Five studies reported on more than one intervention.

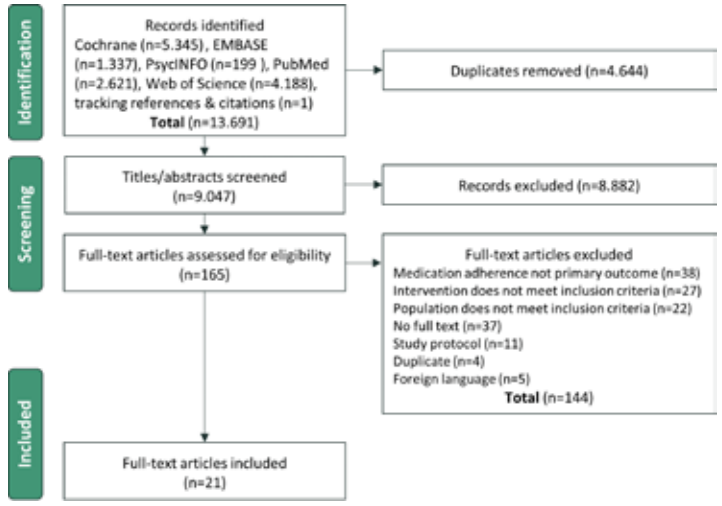

Figure 1. PRISMA flow diagram of study search and selection.

Risk of bias assessment

Fifteen studies had a positive score on at least five domains and were regarded high quality studies as shown in figure 2. Two studies had the lowest score with two out of seven domains scored as positive.

Figure 2. Summary of risk of bias assessment using the Cochrane Collaboration's tool for assessing risk of bias.

Description of study population

Over half of the studies, 13 out of 22, included long-term medication for cardiovascular disease and/or diabetes. Seven studies focussed on other, single long-term conditions, leaving two studies that looked at any long-term conditions where long-term medication was in use.

The smallest study reported on 70 participants at baseline and the largest study involved 21,752 participants.

Description of study design

Two studies looked at the initiation of therapy, the first stage of medication adherence. Twenty studies looked at the second stage (i.e. implementation phase) of medication adherence, leaving no studies to cover the final stage (i.e. discontinuation phase) of medication adherence as primary outcome.[4] Follow-up assessment ranged from one to twelve months. The primary medication adherence outcome of each of the studies was mainly assessed objectively using medication monitoring devices, pharmacy prescription data and serum levels. The remaining six studies measured adherence subjectively with validated self-report questionnaires (e.g., Immunosuppressant Therapy Adherence Instrument (ITAI)).

Description of eHealth interventions and intervention strategies

Twenty-nine different interactive eHealth interventions were evaluated as shown in table 1. Most (21/29, 72%) interventions specified using a (mobile) phone for either calling, texting or mobile applications.

Most (25 out of 29) interventions were aimed at the patient, three interventions were aimed at the caregiver and another was aimed at either patient or caregiver.

Sixteen interventions were provided through automated software without interference of a healthcare professional: six mobile apps, five monitoring devices, three SMS and/or IVR interventions and two e-training modules through an online portal. Another seven interventions were provided through automated software in combination with tele-feedback by a healthcare professional or caregiver: four monitoring devices, two IVR or SMS interventions and one e-training. The six remaining interventions were telephone calls performed by healthcare professionals.

Regarding intervention strategies, nearly all (23/29, 79%) interventions aimed at informing and educating patients and just over half (15/29, 52%) sought to support patients by providing assistance and encouragement. All other strategies (e.g., teaching skills, facilitating communication and/or decision making) were less frequently applied (see Supplementary Figure 1).

Effectiveness of eHealth interventions on medication adherence

Overall, 17 interventions yielded a significant improvement of medication adherence compared to the control group (see Table 1). For 12 interventions an effect size (Cohen's D) could be calculated; Cohen's D ranged from -0.03 to 4.72. Seven interventions reported at least a small effect size (Cohen's D ≥ 0.2).

Table 1. Characteristics of the eHealth interventions

1st author (year)	medication	intervention arm (n)	control arm (n)	follow-up (in weeks)	mode of adherence feedback	description of the intervention	adherence measure (range)	results on medication adherence	significance of effect [a]
Initiation phase									
Cizmic (2015)	bisphosphonates	127	118	4	IVR	An IVR call focussing on known reasons for not initiating therapy. If the medication was not picked up 7 days after receiving the call, a reminder letter was sent.	fill 1st prescription (0 – 100%)	48.8% of the intervention group filled their 1st prescription compared to 30.5% of the control group [OR 2.17; 95% CI 1.29–3.67].	+
O'connor (2014)	anti-hypertensives or medication for lowering blood glucose or cholesterol	1220	1158	9	call	A single protocol-structured telephone call from an interventionist using positive reinforcement and probing for reasons of nonadherence.		83.6% of the intervention group filled their 1st prescription compared to 84.2% of the control group [OR 0.94; 95% CI 0.79–1.11].	-
Implementation phase									
Levine (2019)	tacrolimus	38	50	13	app	Transplant Hero is an interactive alarm to remind patients to take their medications as well as provide educational content.	serum level (0 – 100)	The coefficient of variability (standard deviation / mean * 100) of tacrolimus levels was 33.0 for the intervention and 32.8 for the control group.	-
		20			app & smart-watch	Transplant Hero (see above) combined with a smartwatch that displayed the reminder notifications.		The coefficient of variability was 33.8 for the intervention and 32.8 for the control group.	-
Contreras (2018)	anti-hypertensives	73	75	52	app	The AlerHTA app aimed to promote health education in hypertension and remind for both appointments and medication intake time.	bottle openings (0 – 100%)	Average daily adherence was 86.3% for the intervention and 62.7% for the control group [Cohen's D = 4.72].	+
Kessler (2018)	statins	51	34	26	device	A wireless pill bottle generated an alert message, sent to the participant, if the participant missed medication the previous day and on one or both of the two prior days.		Average daily adherence was 52.9% for the intervention and 36.0% for the control group [Cohen's D = 0.70].	+
		46				A wireless pill bottle generated an automated alert message (see above), sent to the participant and a designated caregiver.		Average daily adherence was 54.5% for the intervention and 36.0% for the control group [Cohen's D = 0.70].	+
Montale-scot (2019)	apixaban	579	583	24	e-training	An education program consisting of an education booklet, one or more reminder tools chosen by the participant and access to a telephone clinic.		Average daily adherence was 91.9% for the intervention and 91.6% for the control group [Cohen's D = 0.02].	-
Reese (2016)	statins	67	67	13	device	PROMOTE: a wireless pill bottle generated a weekly adherence report in which the patient's adherence was compared to other patients.		Average daily adherence was 77% for the intervention and 75% for the control group.	-
						PROMOTE: a wireless pill bottle generated a weekly adherence report.		Average daily adherence was 71% for the intervention and 75% for the control group.	-
Reese (2016)	statins	50	50	13	device	SUPPORT: a wireless pill bottle generated a daily adherence report.		Average daily adherence was 73% for the intervention and 79% for the control group.	-
						SUPPORT: a wireless pill bottle generated a weekly adherence report.		Average daily adherence was 75% for the intervention and 79% for the control group.	-
						SUPPORT: a wireless pill bottle generated an email alert if the patient missed a dose the previous day.		Average daily adherence was 75% for the intervention and 79% for the control group.	-
Reese (2017)	tacrolimus	40	40	26	device	A wireless pill bottle generated an alert when medication was due and patients could select additional reminders like texts, calls or emails.		Average daily adherence (during final 90 days) was 78% for the intervention and 55% for the control group [mean difference = 23%, 95% CI 0.09–0.37].	+
		40				A wireless pill bottle generated an alert (see above). If adherence decreased to <90% in a 14-day period, study coordinator would call patient and notify involved HCPs.		Average daily adherence (during final 90 days) was 88% for the intervention and 55% for the control group [mean difference = 33%, 95% CI 0.20–0.46].	+
Svendsen (2018)	calcipotriol/ betamethas-one foam	68	66	4	app	An app which provided once-daily reminders and information on number of treatment applications and amount of prescribed foam applied.		66% of the intervention group was considered adherent compared to 38% of the control group [OR 3.22; 95% CI 1.53–6.80].	+

Abughosh (2016)	RAS-inhibitors	87	99	26	call	A brief telephone intervention by pharmacists to remind the patients of their overdue refill and to identify potential adherence barriers.	PDC (0 – 100%)	PDC was 58% for the intervention and 29% for the control group [Cohen's D = 1.32].	+
Abughosh (2017)	RAS-inhibitors	248	495	26	call	Six motivational interviewing phone calls by pharmacy students to identify potential adherence barriers and provide guidance to address these barriers.		PDC was 66% for the intervention and 57% for the control group [Cohen's D = 0.26].	+
Choudhry (2018)	anti-hypertensives or medication for lowering blood glucose or cholesterol	2038	2040	52	call	Tailored telephone consultation to develop a shared plan to improve adherence and disease control. At six- and nine-months progress reports were mailed.		PDC was 46.2% for the intervention and 42.1% for the control group [Cohen's D = 0.12].	+
Ducoulombier (2015)	bisphosphonates & strontium ranelate	79	85	52	call	Bimonthly telephone follow-up to enhance patient adherence by motivating patients to maintain good adherence, detecting difficulties in compliance and recalling the importance of continuing the treatment.		65% of the intervention group was considered adherent compared to 33% of the control group [OR 3.71; 95% CI 1.94–7.07].	+
Kooij (2016)	bisphosphonates, RAS-inhibitors & statins	2008	2914	52	call	Telephone counselling 7–21 days after the start of therapy assessing practical and perceptual barriers and providing information and motivation.		PDC was 81% for the intervention and 76% for the control group [Cohen's D = 1.34].	+
Vollmer (2014)	RAS-inhibitors & statins	7247	7255	52	IVR	An IVR call when (over)due for a refill providing patient education and refill support.		PDC was 58% for the intervention and 56% for the control group [Cohen's D = 2.09].	+
		7250				In addition to IVR calls (see above), a reminder letter was sent if they were 60-89 days overdue, a call was made if they were ≥90 days overdue and their primary care provider informed. Patients also received a personalised health report, a pill organiser, and bimonthly mailings.		PDC was 59% for the intervention and 56% for the control group [Cohen's D = 2.14].	+
Claborn (2014)	Highly Active Anti-Retroviral Therapy	47	50	4	e-training	eLifeSteps: a single-session, self-paced multimedia intervention tackling practical and psychological adherence barriers accompanied with a workbook.	AACTGAI (0 – 100%)	Adherence was 80.5% for the intervention group and 81.4% for the control group [Cohen's D = -0.03].	-
Cote (2018)	immuno-suppressants	35	35	26	e-training	Transplant-TAVIE was composed of three interactive Web-based sessions by a virtual nurse aimed at developing and reinforcing self-management skills required for medication intake.	ITAI (0 – 12)	Mean ITAS score was 11.7 in the intervention and 11.3 in the control group [Cohen's D = 0.30].	-
Kamal (2015)	preventive medication for stroke	100	100	8	SMS	SMS4stroke sent automated customised SMS reminders to either patient or caregiver.	MMAS (0 – 8)	Mean MMAS score was 7.4 in the intervention and 6.7 in the control group [Cohen's D = 0.62].	+
Kamal (2018)	statins and anti-platelets	99	98	13	IVR & SMS	Daily IVR call services, daily prescription tailored medication reminders and once weekly life style modification messages.	MMAS (0 – 8)	Mean MMAS score was 7.29 in the intervention and 7.07 in the control group [Cohen's D = 0.03].	-
Mira (2014)	all medication allowed, >2	51	49	13	app	A tablet-based medication self-management app (ALICE) with medication reminders and medication information such as pictures, interactions, storage instructions and common errors in medication use.	MMAS-4 (0 – 8)	Mean MMAS score was 7.4 in the intervention and 7.3 in the control group [Cohen's D = 0.12] (not corrected for baseline).	+
Morawski (2018)	anti-hypertensives	209	202	12	app	The MediSafe app is a medication reminder app with additional functions like adherence reports, tracking of measurements and peer support.	MMAS (0 – 8)	Mean MMAS score was 6.3 in the intervention and 5.7 in the control group [Cohen's D = 0.35].	+

Abbreviations: RAS = renin angiotensin system, PDC = percentage of days covered, IVR = interactive voice response, SMS = short text messaging, AACTGAI = Adult AIDS Clinical Trials Group Adherence Instrument, ITAI = Immunosuppressant Therapy Adherence Instrument, MMAS = Morisky Medication Adherence Scale, + = $p < 0.05$ favouring intervention, - = $p > 0.05$ (no significant difference between groups). [a] As reported by the authors.

Heterogeneity of the studies and interventions precluded meta-analysis on the effectiveness of eHealth interventions on medication adherence. Therefore a best-evidence synthesis was conducted (table 2). There was strong evidence for a positive effect for SMS and/or IVR, mobile applications and calls as mode of adherence feedback. The evidence for e-training was weak and for monitoring devices conflicting.

Table 2. Results of the best evidence synthesis

mode of adherence feedback	quality	significance of effect	level of evidence
monitoring device	9 HQ interventions 0 LQ interventions	+, +, +, +, -, -, -, -, -	conflicting evidence
SMS and/or IVR	5 HQ interventions 0 LQ interventions	+, +, +, +, -	strong evidence for a positive effect
mobile application	3 HQ interventions 3 LQ interventions	+, +, + +, -, -	strong evidence for a positive effect
call	4 HQ interventions 2 LQ interventions	+, +, +, - +, +	strong evidence for a positive effect
e-training	1 HQ intervention 2 LQ interventions	- -, -	weak evidence for no effect

Abbreviations: SMS = short text messaging; IVR = interactive voice response; HQ = high quality; LQ = lower quality; + = $p < 0.05$ favouring intervention; - = $p > 0.05$ (no significant difference between groups). In grading the level of evidence low quality studies were disregarded when there were two or more high quality studies.

In the post-hoc sensitivity analysis the criteria for a high-quality study were more stringent (6 out of 7 instead of 5 out of 7 domains graded as low risk of bias). The sensitivity analysis showed that the strong evidence for a positive effect for SMS and/or IVR as mode of adherence feedback remained whereas the evidence turned to conflicting for interventions delivered through mobile applications and calls. (*see Supplementary Table 1*)

The level of evidence of the intervention strategies was also assessed. There was strong evidence for a positive effect of strategies to teach skills, to facilitate communication and/or decision making and to improve health care quality. For all other intervention strategies (e.g., to support, to inform and educate) there was conflicting evidence. (*Supplementary Table 2*)

Discussion

This systematic review examined the effectiveness of eHealth interventions to improve medication adherence in patients using long-term medication published between 2014 and 2019. A majority, 17 out of 29 interactive interventions, had a significant positive effect on medication adherence. There was strong evidence for a positive effect for interventions using SMS and/or IVR, mobile applications and calls as mode of adherence feedback. Intervention strategies to teach skills, to improve health care quality and to facilitate communication and/or decision making showed strong evidence for a positive effect. Overall, this review supports the expectation that eHealth interactive interventions can be effective to improve medication adherence.

This study showed strong evidence for a positive effect on medication adherence of eHealth interventions across various channels, including SMS, IVR, mobile applications and calls. Our findings add robustness to the positive effect of eHealth interventions provided by

previous systematic reviews and meta-analyses.[44–49] Where those authors were cautious with interpreting their findings because of low quality studies, small sample sizes and short follow-up, many studies we included were of high quality (22/29), had sample sizes of 100 patients or more (19/29) and follow-up of at least six months (14/29). IVR interventions that included information about health consequences suggest a stronger behavioural change, including medication-taking behaviour.[49] This review confirms these findings as the included IVR interventions all contained information on the consequences of (not) taking medication as prescribed. For call, mobile application and SMS interventions it remains unclear whether there are intervention elements (e.g., content, intervention design or extent of tailoring) that contribute to increased medication adherence since most eHealth interventions are multicomponent and elements vary widely across interventions.[44,46,48]

We found a lack of convincing evidence for interventions applying an electronic monitoring device or e-training. In contrast, Van Heuckelum et al50 found a positive effect for interventions using monitoring device feedback. In our review all interventions coupled their electronic monitoring devices to the same (Way To Health) communication platform which could be a possible explanation. Yet, Van Heuckelum et al[50] also included interventions that gave face-to-face feedback on adherence data collected by monitoring devices. They showed that these interventions were effective whereas those who applied tele-feedback were not. This suggests that feedback on tele-monitoring of medication adherence is best given face-to-face.

In this review we provide evidence for interactive adherence interventions aimed at teaching skills such as self-management programs, aimed at improving health care quality by coordinating medication adherence care between professionals and aimed at facilitating communication and/or decision making between patient and health care professional. These results should be interpreted with caution because interventions were multi-faceted and combined different. It is not possible to assign success to a single strategy within a multi-faceted intervention. Nonetheless the effective strategies we identified in this review suggest to be good starting points for development or selection of interventions.

Noteworthy, the included studies in our review using eHealth interventions to address medication adherence reflect two distinct patient populations namely the large patient population (e.g., metabolic and cardiovascular disease) and the population where optimal medication adherence is critical (e.g., HIV, organ transplant recipients). Applying eHealth to address medication adherence can be advantageous for both populations albeit for different reasons. eHealth interventions can be accessible for large patient populations, giving health care professionals a large outreach with limited resources. For populations where optimal medication adherence is critical, eHealth interventions can be tailored to patients' specific needs and provide continuous support.

Where others found a lack of high quality studies and stressed the importance of improving study quality[3,9,16], this review included 15 (out of 23) high quality studies. The increase in quality presumably is a direct consequence of better reporting and study designs. We chose the Cochrane risk of bias tool (version 1) to assess study quality. This tool mainly focusses on internal validity and does not cover all aspects of study design. We found flaws in study design that were not covered by the Cochrane risk of bias tool like absence of sample size calculation, selection bias and disputable (adherence) outcomes. This could have (negatively) affected the implications of the results.

Our best evidence synthesis was limited to medication adherence as primary outcome and did not consider other clinical outcomes. Although improvement on clinical outcomes is the ultimate treatment goal, we had two reasons to focus on medication adherence. First of all, medication adherence can be measured across conditions making it well suited to evaluate effectiveness of interventions regardless of the long-term condition. Secondly, to be certain that the observed effect on clinical outcomes is a consequence of improved medication adherence this needs to be established first. Previous systematic reviews found no direct relationship between increased medication adherence and positive clinical outcomes.[3,45,50]

Although other taxonomies (e.g, Abraham[51], Demonceau[52], Kini[7]) could have been used to categorise strategies applied by interventions, they show many conceptual similarities with Löwe's taxonomy. We therefore used Löwe's taxonomy as it is specific for adherence interventions with clear examples of each strategy.

We were surprised to find many interactive eHealth interventions that use technologies published in the 20th century. Although technology changes, the techniques applied are very similar. To be able to build upon data and lessons learnt from older technologies, cross links between similar techniques need to be made. For example, determining whether the effectiveness of text messaging also holds true for other forms of messaging like WhatsApp or WeChat. As technological developments are very fast-paced, eHealth interventions continuously change and adapt. This high turnaround speed makes it hard to thoroughly investigate adherence interventions that remain unchanged with a follow-up of at least six months. Therefore, study designs that implement continuous evaluation of interventions are preferred. Even more, the relation between intervention exposure and changing medication taking behaviour needs to be addressed. In this review, intervention exposure ranged from a single call of a few minutes to daily messages for months. Dose-response studies can provide insight into the relation between exposure and behaviour change.

Conclusion

We found that a majority of interactive eHealth interventions is effective in improving adherence to long-term medication. Interventions that support behaviour change by improving patient's treatment involvement and skills are most promising. While most eHealth interventions were multi-faceted, even simple eHealth technologies like text messaging and telephone calls can be effective in promoting medication adherence in a wide variety of patient populations.

Conflicts of Interest

All authors declare no conflict of interest.

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Supplementary material S1. MEDLINE search strategy

eHealth interventions

(telemedicine[MH] | ehealth[tiab] | e-health[tiab] | electronic health[tiab] | telemedicine[tiab] | telehealth[tiab] | mhealth[tiab] | m-health[tiab] | mobile health[tiab] | emedicine[tiab] | e-medicine[tiab] | etherap*[tiab] | health technolog*[tiab] | information technolog*[tiab] | communication technolog* [tiab] | mobile tech*[tiab] | platform[TiAb] | telecare[tiab] | tele-care [tiab] |telepharmacy [tiab] | telecommunic*[tiab] | telemonitoring [tiab] |remote monitor* [tiab] | remote consult* [tiab]| telephone[MH] | phone[TiAB] | smartphone*[tiab] | mobile device*[tiab] | personal digital assistant[tiab] | pda[tiab] | wearable*[tiab] | smartwatch*[tiab] | smart-watch*[tiab] | computers[MH] | computers[TiAb] | computer[TiAb] | internet[MH] | internet[TiAb] | web[TiAb] | website [tiab] | e-mail[TiAb] | email[TiAb] | electronic mail[TiAb] |online[TiAb] | wireless[TiAb] | bluetooth[tiab] | blue tooth[tiab] | mobile applications[MH] | apps[tiab] |app[tiab]| mobile application[tiab] | interactive media[tiab] | social media[tiab] | instant messag*[tiab] | IM[tiab] | text messaging[MH] | text messag*[tiab] | SMS[tiab] | multimedia[tiab] | MMS[tiab] | chat[tiab] | social network[tiab] | teleconference*[tiab] | videoconference*[tiab] | virtual[tiab] | digital[TiAb] | (tablet*[TiAb] AND (mac | ipad | android | Microsoft | windows)))

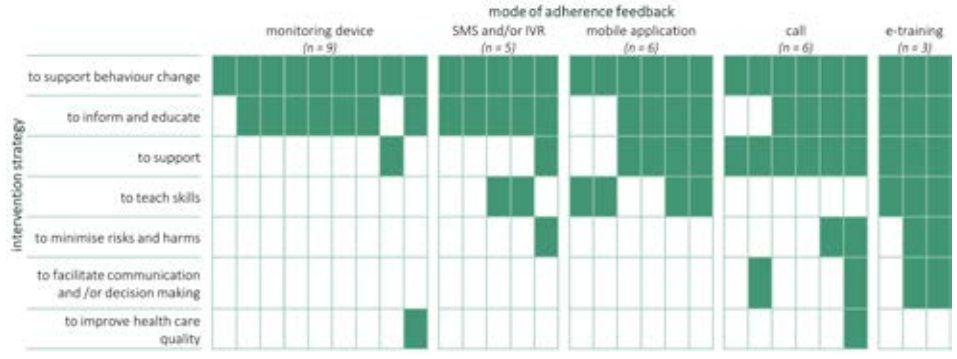
Medication adherence

(medication adherence[MH] | patient compliance[MH] | medication compliance[TW] | medication non compliance[TW] | medication noncompliance[TW] | medication adherence[TW] | medication non adherence[TW] | medication nonadherence[TW] | medication adherance[TW] | medication non adherance[TW] | medication nonadherance[TW] | medication persistence[TW] | medication non persistence[TW] | medication nonpersistence[TW] | medication persistance[TW] | medication non persistance[TW] | medication nonpersistance[TW] | medicine compliance[TW] | medicine non compliance[TW] | medicine noncompliance[TW] | medicine adherence[TW] | medicine non adherence[TW] | medicine nonadherence[TW] | medicine adherance[TW] | medicine non adherance[TW] | medicine nonadherance[TW] | medicine persistence[TW] | medicine non persistence[TW] | medicine nonpersistence[TW] | medicine persistance[TW] | medicine non persistance[TW] | medicine nonpersistance[TW] | medical compliance[TW] | medical non compliance[TW] | medical noncompliance[TW] | medical adherence[TW] | medical non adherence[TW] | medical nonadherence[TW] | medical adherance[TW] | medical non adherance[TW] | medical nonadherance[TW] | medical persistence[TW] | medical non persistence[TW] | medical nonpersistence[TW] | medical persistance[TW] | medical non persistance[TW] | medical nonpersistance[TW] | drug compliance[TW] | drug non compliance[TW] | drug noncompliance[TW] | drug adherence[TW] | drug non adherence[TW] | drug nonadherence[TW] | drug adherance[TW] | drug non adherance[TW] | drug nonadherance[TW] | drug persistence[TW] | drug non persistence[TW] | drug nonpersistence[TW] | drug persistance[TW] | drug non persistance[TW] | drug nonpersistance[TW] | drugs compliance[TW] | drugs non compliance[TW] | drugs noncompliance[TW] | drugs adherence[TW] | drugs non adherence[TW] | drugs nonadherence[TW] | drugs adherance[TW] | drugs non adherance[TW] | drugs nonadherance[TW] | drugs persistence[TW] | drugs non persistence[TW] | drugs nonpersistence[TW] | drugs persistance[TW] | drugs non persistance[TW] | drugs nonpersistance[TW])

Randomised Controlled Trial

(randomized controlled trial [PT] | clinical trials as topic [mesh: noexp] | randomized [tiab] | randomised [tiab] | randomly [tiab] | placebo [tiab] | usual care [tiab]| trial [ti])

Supplementary Figure 1. Strategies applied by the eHealth interventions for each mode of feedback



Supplementary Figure 1. Strategies applied by the eHealth interventions for each mode of feedback

Supplementary Table 1. Sensitivity analysis

mode of adherence feedback	quality	significance of effect	level of evidence
monitoring device	9 HQ interventions 0 LQ interventions	+, +, +, +, -, -, -, -, -	conflicting evidence
SMS and/or IVR	2 HQ interventions 3 LQ interventions	+, + +, +, -	strong evidence for a positive effect
mobile application	0 HQ interventions 6 LQ interventions	 +, +, +, +, -, -	conflicting evidence
call	2 HQ interventions 4 LQ interventions	+, - +, +, +, +	conflicting evidence
e-training	1 HQ intervention 2 LQ interventions	- -, -	weak evidence for no effect

Abbreviations: SMS = short text messaging; IVR = interactive voice response; HQ = high quality; LQ = lower quality; + = p < 0.05 favouring intervention; - = p > 0.05 (no significant difference between groups). In grading the level of evidence low quality studies were disregarded when there were two or more high quality studies.

Supplementary Table 2. Level of evidence of intervention strategies

intervention strategy	quality	significance of effect	level of evidence
to support behaviour change	22 HQ interventions 7 LQ interventions	+, +, +, +, +, +, +, +, +, +, +, +, +, +, -, -, -, -, -, -, -, -	conflicting evidence
to inform and educate	16 HQ interventions 7 LQ interventions	+, +, +, +, +, +, +, +, +, -, -, -, -, -, -	conflicting evidence
to support	8 HQ interventions 7 LQ interventions	+, +, +, +, +, +, -, -, -	conflicting evidence
to teach skills	6 HQ interventions 3 LQ interventions	+, +, +, +, +, +	strong evidence for a positive effect
to minimise risk and harms	2 HQ interventions 3 HQ interventions	+, - +, -, -	conflicting evidence
to facilitate communication and/or decision making	2 HQ interventions 2 LQ interventions	+, + -, -	strong evidence for a positive effect
to improve health care quality	2 HQ interventions 0 HQ interventions	+, +	strong evidence for a positive effect

Abbreviations: HQ = high quality; LQ = lower quality; + = p < 0.05 favouring intervention; - = p > 0.05 (no significant difference between groups). In grading the level of evidence low quality studies were disregarded when there were two or more high quality studies.

Chapter 5

A serious puzzle game to enhance adherence to anti-rheumatic drugs in rheumatoid arthritis patients – systematic development using Intervention Mapping

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Abstract

Background
Patients' implicit attitudes towards medication need and concerns may influence their adherence. Targeting these implicit attitudes by combining game-entertainment with medication-related triggers might improve medication adherence in rheumatoid arthritis (RA) patients.

Objective
To describe the systematic development of a serious game to enhance adherence to anti-rheumatic drugs using Intervention Mapping.

Methods
A serious game was developed using the Intervention Mapping framework guided by a multidisciplinary expert group which proceeded along six steps: (1) exploring the problem by assessing the relationship between medication adherence and implicit attitudes, (2) defining change objectives, (3) selecting evidence-based behaviour change techniques that focussed on adjusting implicit attitudes, (4) designing the intervention, (5) guaranteeing implementation by focussing on intrinsic motivation and (6) planning a scientific evaluation.

Results
Based on the problem assessment and guided by the Dual-Attitude Model, implicit negative and illness related attitudes of RA patients were defined as the main target for the intervention. Consequently, the change objective was: 'After the intervention, participants have a more positive attitude towards anti-rheumatic drugs'. Attention bias modification, evaluative conditioning and goal priming were the techniques chosen to implicitly target medication needs. These techniques were redesigned into medication-related triggers and built in the serious puzzle game. Thirty-seven RA patients tested the game at several stages. Intrinsic motivation was led by the self-determination theory and addressed the three needs competence, autonomy and relatedness. The intervention will be evaluated in a randomised clinical trial that assessed the effect of playing the serious game on anti-rheumatic drug adherence.

Conclusion
We systematically developed a serious game application to enhance adherence to anti-rheumatic drugs among RA patients using the Intervention Mapping framework. This article could serve as a guideline for other healthcare providers when developing similar interventions.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterised by symmetric chronic polyarthritis which, if untreated, leads to pain, joint damage and decreased quality of life.[1,2] The cornerstone of RA treatment is the use of anti-rheumatic drugs (DMARDs – disease modifying antirheumatic drugs) which reduces disease activity, radiological progression and increases patient's functioning.[3,4] These benefits are not reached when patients are nonadherent to their long-term therapy.[5,6] It is estimated that around one third of the RA patients is nonadherent to DMARD therapy.[7–9] As such, achieving medication adherence remains a major challenge for a substantial proportion of RA patients.

Understanding medication nonadherence and its causes helps to identify targets for the development of adherence interventions. Practical barriers (e.g. forgetfulness, costs) and patient's attitudes towards medication (e.g. balance between necessity and concerns) are associated with medication nonadherence.[10,11] As a consequence these factors have frequently been the main target of interventions aiming to improve nonadherence.[12] Unfortunately adherence interventions have been only partly effective.[13–16]

Part of this ineffectiveness might be because medication taking behaviour is not yet fully elucidated. Behavioural intentions such as taking medication are driven by a person's explicit (conscious) and implicit (unconscious) attitudes.[17] These attitudes do not necessarily have to be congruent. Someone might explicitly say medication helps alleviate symptoms but implicitly regard medication as chemical rubbish.[17,18] Habitual behaviour, like medication taking behaviour, happens mainly on an unconscious level and is more likely to be guided by implicit attitudes.[19] Therefore targeting implicit attitudes might be an effective strategy to improve medication adherence.

Implicit attitudes are targeted by reinterpretation training, i.e., exercising the brain to interpret a stimulus differently.[20] This can, for instance, be achieved by performing tasks that lead to pairing of a medication stimulus with another, positive stimulus.[21] Such a reinterpretation training needs rigorous and repetitive exercising to be successful or, in other words, a multi-dose intervention is required. eHealth can be a suitable mode of delivery for a multi-dose intervention as it is easily accessible and allows patients to perform these tasks at a convenient time and place. Retention of a multi-dose intervention is best achieved when participants are intrinsically motivated to prevent dropout prior to the effect of the intervention being reached.

Motivation can be maintained by formatting the intervention as serious game.[22,23] Serious games are games that intend to entertain and to achieve at least one additional goal.[22] In order to motivate patients to play the serious game, the self-determination theory may be used to guide serious game development. According to this theory, intrinsic motivation is most likely to occur when three needs are satisfied: competence, autonomy and relatedness.[24,25] A serious game can satisfy these three needs creating intrinsically motivated players that will adhere to a multi-dose intervention. As a result, serious games can positively influence behaviour, even by targeting implicit attitudes.[26,27]

Taken together, the present paper describes the systematic development of a serious game using the Intervention Mapping framework.[28] This serious game should provide entertainment as well as positively influence medication adherence by targeting implicit attitudes.

Methods

Intervention Mapping (IM) was used to systematically develop the intervention.[29] IM considers and applies theory and empirical evidence to maximise the effectiveness and usability of the intervention, covers the complete range from problem identification to scientific evaluation and ensures the intervention is compatible with the target population.[29] A complex problem like medication taking behaviour demands a multidisciplinary approach. Therefore the IM process was guided by meetings of an expert group consisting of a pharmacist, rheumatologist, rheumatology nurse, psychologist, innovation manager, representative of the pharmaceutical industry and game developer Games for Health®.

Intervention Mapping framework

The IM framework comprises six steps where each step leads to a product that guides the subsequent step. See table 1 for an overview of IM steps with associated tasks and intermediate development products. The goal of the first step is to assess the health problem. Main task in this step is to identify the determinants for the at-risk population of the problematic behaviour (nonadherence). Step 2 builds on the previous step by using the identified determinants to formulate the change objectives. The change objectives specify who and what will change as a result of the intervention. In step 3 theory-informed methods and practical strategies are searched for that are most likely to accomplish the formulated change objectives. During step 4 the intervention is produced based on the outcomes of the previous steps and refined after pilot testing. The goal of step 5 is to increase programme adoption, implementation and maintenance by creating an implementation plan. Finally, in step 6 the effect of the intervention is evaluated to ensure that the desired behavioural outcome is achieved.

Table 1. Intervention mapping steps with associated tasks and applied methodology.

Intervention mapping steps	Intervention mapping tasks	Methods
Step 1: Logic model of the problem	Describe the context for the intervention Identify determinants for the at-risk population of the problem	PubMed literature search on determinants of nonadherence (2010-2015) Explorative study in 52 patients on relation between attitudes and medication adherence
Step 2: Program outcomes and objectives	State expected outcomes for behavior Specify performance objectives for behavioral outcomes Select determinants for behavioral outcomes Create a logic model of change	Multiple expert group discussions (both face-to-face and electronic)
Step 3: Program design	Generate program themes, components, scope, and sequence Choose theory- and evidence-based change methods Select or design practical apps to deliver change methods	Literature search and expert opinion on behavior change techniques Multiple expert group discussions Iterative game development
Step 4: Program production	Refine program structure and organization Prepare plans for program materials Draft messages, materials, and protocols Pretest, refine, and produce materials	Iterative game development Stage 1 user testing: 54 DMARD users played at home in 2 rounds for 2 weeks Stage 2 user testing: 8 DMARD users performed a live walkthrough
Step 5: Program implementation plan	State outcomes and performance objectives for program use Construct matrices of change objectives for program use	Iterative game development guided by self-determination theory
Step 6: Evaluation plan	Write effect and process evaluation questions Develop indicators and measures for assessment Specify the evaluation design	Develop a randomized clinical trial study protocol to examine effectiveness on DMARD adherence (GAMER [Gaming for Adherence to Medication using E-health in Rheumatoid arthritis patients] study)

1. Logic model of the problem

As first step the context of the intervention (population and setting) is described. Next, two methods were used to identify determinants for patients with rheumatic disease being at-risk for nonadherence: 1) a literature search and 2) an explorative study on the implicit and explicit determinants toward DMARD use performed by research team members.[30]

The literature search was performed in PubMed in 2015 and focussed on recent (2010 – 2015) studies, including systematic reviews, using the MeSH terms ‘medication adherence’ and ‘rheumatic diseases’ coupled with free text term ‘determinant’. Both primary studies and systematic reviews were included. All determinants mentioned in the selected studies and their association with medication adherence were collected and split into nonmodifiable and modifiable factors. Nonmodifiable factors aid in identifying the target population whereas modifiable factors aid in identifying target behaviour.

Habitual behaviour, like medication taking behaviour, is likely to be guided by implicit attitudes as well as explicit attitudes.[19] However it is unclear how explicit and implicit attitudes relate

to medication adherence. Therefore this was explored by research team members in a sample of RA patients and published elsewhere.[30] In short, the sample consisted of 52 patients on oral methotrexate therapy from the Sint Maartenskliniek - a Dutch tertiary rheumatology clinic. Patients were approached when collecting their medication refill and assessment took place immediately after providing informed consent. Patients performed a computerised task (SC-IAT) to measure the implicit measures of medication attitudes and associations which is a well-established and valid measure of implicit associations.[31] Additionally they completed a questionnaire on demographics and questionnaires on explicit attitudes and associations (Beliefs about Medication Questionnaire (BMQ)[32–35]) and medication adherence (Compliance Questionnaire on Rheumatology (CQR)[36–38]), both proven valid and reliable in patients with rheumatoid arthritis. Clinical outcomes (Erythrocyte Sedimentation Rate and C-Reactive Protein) were obtained from patients' medical file. Because of the explorative character of this study, Pearson's correlations were used to examine the relationship between patients' explicit and implicit attitudes, associations, beliefs, adherence, clinical outcomes and demographics.

2. Programme outcomes and objectives

The behavioural outcome of the intervention is to become adherent and/or maintain DMARD adherence. As the patient is the one who has the main influence on medication-taking behaviour we only defined change objectives at the patient level. As a result there are no change objectives at the interpersonal, organisational, communal or societal level. The change objective of the intervention was guided by the outcomes of step 1 and established through multiple (electronic) discussions of the expert group through an organic iterative process.

3. Programme design

The fundament of the behavioural change for our intervention was the Dual-Attitude model. The Dual-Attitude model postulates that implicit and explicit attitudes coexist and do not necessarily have to be congruent.[17,30] When dual attitudes exist, the implicit attitude is activated automatically, whereas the explicit one requires more capacity and motivation to retrieve from memory. As such, habitual behaviour like medication taking behaviour is more likely to be guided by implicit attitudes.[19] Implicit attitudes can be targeted by a behaviour change technique called bias modification.[20] Google Scholar and Pubmed were narratively searched for suitable behaviour change techniques. The search terms consisted of the free text words 'behaviour change technique', 'bias modification' and 'health'. To narrow the search results, the terms 'review' and 'overview' were added to the search strategy. The behaviour change techniques shown to effectively address health behaviours were selected and presented to the game developer for applicability. Next, the game type was carefully chosen to suit the context (target population and setting) of the intervention from step 1.

4. Programme production

The serious game was developed using an iterative design process. Based on the theory of the previous steps, the expert group prepared the outline of the intervention components in multiple sessions. Games For Health® used their expertise to create the components within the technical possibilities and merged them to form the game. The game was tested by patients and the feedback used to adapt the game after which this process was repeated. As a result, the final product is a practical interpretation of the theory. The test-panel members were representative for the target group and recruited from the Sint Maartenskliniek, Nijmegen, The Netherlands. They were patients aged 16 years or older that used DMARDs.

Ethical approval for user-testing was asked for and waived by the local medical research ethics committee of Arnhem-Nijmegen under code 2017-3355. A random sample of 500 patients using DMARDs received an invitation with informed consent enclosed through mail. Additionally, participants needed to possess a tablet and be proficient in the Dutch language. Stage one consisted of two rounds of two weeks of user testing at home after which data on acceptability was collected. Acceptability was determined using the Technology Acceptance Model (TAM) as underpinning which is a well-established model for usability evaluation of eHealth.[39–41] This model postulates that ease of using a technology influences the perceived usefulness and the attitude toward using and together form the behavioural intention to use a technology which leads to actual use. Ease of use was measured using the System Usability Score questionnaire taken directly from the TAM.[39,42,43] The perceived usefulness of a game was operationalised as enjoyment and assessed using the GameFlow questionnaire which has been successfully applied to distinguish between the high-rated and low-rated games and identify why one succeeded and the other failed.[44,45] Attitude toward using was assessed using four questions of the user version of the Mobile Application Rating Scale (uMARS) which is a simpler end-user version of the validated MARS.[46,47] The questions of the uMARS that captured the overall feeling of the app and its potential use were selected by authors BP and BVDB until consensus was reached. All other questions were omitted as they related to other aspects of mobile applications and even overlapped with ease of use and usefulness. Actual use was collected using Google Analytics and determined to be time played and number of sessions. In addition, participants were asked for their overall experience and suggestions for improvement (open-ended questions) to inform the game developers.

Stage two was a live walkthrough where patients performed tasks within the serious game environment under supervision. A team of game developers from Games For Health and author BP observed the participants and took notes. Participants were recruited from players in stage 1 (experienced users) and from the patient-representatives of the Sint Maartenskliniek (new users). Suggestions for improvement were collected with the aim of improving gameplay and increasing retention.

5. Programme implementation plan

Intrinsic motivation is key to ensure adoption and implementation of a serious game. The Self-Determination Theory posits that motivation is a continuum between extrinsic motivation (e.g., external factors such as rewards or grades) and intrinsic motivation (e.g., internal factors such as interest, curiosity or care). Intrinsic motivation can be reliably enhanced by supporting the satisfaction of three psychological needs: competence, autonomy and relatedness.[24,25,48] Competence denotes the experience of mastery. It becomes satisfied when capably engaging in activities and experiencing opportunities for using and extending skills. Autonomy denotes the experience of willpower and willingness without external pressure. Relatedness denotes the experience of bonding and care and is satisfied by connecting to others. In the results section we have described how our serious game addresses these needs.

6. Evaluation plan

To assess whether the developed intervention positively effects DMARD adherence a research proposal was drafted for a multi-centre randomised controlled trial: the GAMER (Gaming for Adherence to Medication using E-health in Rheumatoid arthritis patients) study.

Results

1. Logic model of the problem

The intervention is set within the context of rheumatoid arthritis (RA). RA mainly effects people over 50 years of age and is more common among women.[1] Because most DMARDs are used at home, our adherence enhancing intervention should be utilised in the home setting.

The literature search on determinants of nonadherence resulted in 73 publications of which 12 detailed on determinants of medication adherence in rheumatic diseases.[7,10,56,57,11,49–55] There were no nonmodifiable patient characteristics that indisputably predicted medication nonadherence. Therefore we decided that our intervention should be aimed at all RA patients. The modifiable determinants that remained were psychosocial and therapy-related factors. As our intervention should not interfere with RA treatment, we focussed on psychosocial factors. Supportive evidence was found for the following modifiable psychosocial factors influencing medication adherence: perceived treatment necessity, treatment concerns, satisfaction with care, treatment self-efficacy, coping, practical barriers, social support, disease or treatment understanding, illness beliefs/perceptions and lifestyle. The necessity/concerns balance and practical barriers had the strongest association with medication adherence.[10,51]

As stated in the introduction, behavioural intentions are driven by both explicit (conscious) and implicit (unconscious) attitudes.[17] Habitual behaviour, like medication taking, is guided stronger by implicit attitudes than by explicit attitudes which play a stronger role in conscious (planned) behaviour.[19] To understand the possible role of implicit attitudes regarding medication taking behaviour, we performed an explorative study with 52 patients that showed that explicit attitudes were positive and health related. Implicit attitudes were, however, negative and illness related. Half of the patients displayed explicitly positive but implicitly negative attitudes.[30] The relationship between implicit attitudes and medication adherence is worth being further explored to potentially make interventions more effective.

2. Programme outcomes and objectives

The primary outcome of the intervention is to become adherent and/or maintain DMARD adherence which was defined as taking at least 80% of the prescribed doses. This cut-off is widely used in (RA) adherence research and associated with improved in clinical outcomes in RA.[5]

It is increasingly recognised that medication adherence is not an order from a clinician for the patient to execute ("compliance" to therapy) but requires active patient participation and stimulation (adherence). As a consequence an intervention enhanced with positive affect is more successful in increasing adherence.[58] In addition, the explorative study learned that patients' implicit and explicit attitudes do not correlate and that implicit attitudes are generally negative and illness related. Therefore the expert group considered that reconditioning implicit negative attitudes to more positive ones could shift the necessity/concerns balance. In that light the expert group drafted a change objective that was adjusted and refined over several rounds of discussion. Ultimately this led to the following change objective: 'After the intervention, participants have a more positive attitude towards DMARDs.'

3. Programme design

The explorative study in RA patients performed in step 1 learned that, generally, explicit attitudes are positive and implicit attitudes are negative.[30] To enable change to occur, the expert group aimed at reducing negative explicit attitudes and reinforcing positive implicit attitudes (see table 2). The idea was that the net result of these two actions would be overall a more positive attitude towards medication.

Medication concerns can be targeted by patient education.[12,49] As a result our strategy was to explicitly reduce concerns by educating patients on how to best use DMARDs.

The literature search on bias modifications to change implicit attitudes led to multiple reviews with examples of gamified behaviour change techniques.[20,21] To positively influence the associations between medication beliefs and medication use on an implicit level three mental domains can be addressed: cognition (knowing), affect (feeling) and motivation (willing).[20]

Cognitions/beliefs can be altered using attentional bias modification training.[21] During training, attention is shifted in a positive direction by repetitively drawing attention to positive associations between medication beliefs and medication use. Similarly affect can be modified by training participants to pair medication with another positive stimulus, so called evaluative conditioning. Lastly, motivation can be implicitly targeted by goal priming: passive and unobtrusive activation of people without them being aware of it. Taken together, we applied one explicit and three implicit strategies as underpinning for behaviour change to occur.

Implicit attitudes are activated automatically but, like old habits, are harder to change.[17] As a result, a multi-dose intervention in the form of a serious game was chosen. The expert group identified game types that fit the target population which in the case of RA are mainly women over the age of 50. One of the favourite leisure time activities is solving puzzles and therefore it was decided to develop a serious puzzle game.[59,60]

Table 2. From change objective to intervention strategies—step 3 and step 4 of intervention mapping.

Domain	*Motivation - implicit*	*Affective - implicit*	*Cognitive - implicit*	*Cognitive - explicit*
Step 3 *strategies*	Goal priming: passive, subtle, and unobtrusive activation by external stimuli such that people are not aware of the influence exerted by those stimuli.	Reinforcing the positive valence of DMARD use by strengthening the positive associations through pairing DMARDs with a positive stimulus.	Reinforcing attention toward medication using positive stimuli. Part of the techniques applied are based on attention bias modification training.	Reduce concerns by educating patients on how to best use DMARDs.
Step 4 *game components*	Personalisation of the game Icon characters "Medi and Seintje" Come-and-play reminder Barcode scanner	Personalisation of the game Icon characters "Medi And Seintje" Energising game environment Slide to unlock Visual search	Personalisation of the game Icon characters "Medi and Seintje" Dot-probe task Visual search	Multiple choice medication quiz

4. Programme production

The design of the game environment needed to merge medication and puzzles and simultaneously be positive and energising. The game was named 'Medi & Seintje' which is Dutch wordplay on 'medication' and 'signalling'. Medi and Seintje are icon characters that look like a tablet and capsule, respectively (see Figure 1A). To ensure that participants would relate to the game, game personification was built in. If participants allowed camera use, they could take a picture of themselves and of their medication which was used in the behaviour change techniques (see below).

Secondly, the behaviour change techniques had to be integrated into the puzzle game in such a way that participants would encounter them without being too obtrusive to disturb gameplay. The behaviour change techniques were added to the puzzle environment as so called 'triggers' that allowed participants to open the game or a puzzle. details). These triggers were gamified behaviour change techniques and considered important game components (see Table 1). After completing the trigger at start up, the game offered four puzzle types (see Figure 1C/D), each with three levels of difficulty: crossword, sudoku, wordsearch and tangram. The game environment adhered to the 'Medi & Seintje' theme. A total of five triggers were developed: multiple choice medication quiz, dot-probe task, visual search, slide to unlock (see Figure 1B) and a barcode scanner (see Supplementary Material for more details).

Figure 1. Screenshots of the serious puzzle game
A. Icon characters Medi and Seintje introduce themselves. B. Users are instructed to slide the pill down the screen toward a picture of the user to unlock trigger. C. The puzzle menu showing the 4 puzzle types: crossword, sudoku, word search, and tangram. D. Example of the crossword puzzle screen.

A total of fifty-four DMARD users (11% of the invitations) agreed to test the game at stage 1. Median age was 63 years and median years since diagnosis 10 years. Thirty-three participants were female (61%) and 39 (72%) used their tablet daily. Stage 1 consisted of two rounds where the feedback of round 1 was incorporated in the game before testing in round 2. Of the 52 participants, 39 participants completed the study: nine participants did not download the app (reason unknown), two stopped due to technical issues and two stopped because of medical reasons. In round 1, 19 participants used the app and 22 in round 2 of which 12 in both. On average, in round 1 users played 1.4 sessions per day that lasted 12 minutes and in round 2 users played 1.7 sessions per day that lasted 16 minutes. Although playtime increased, there were no significant differences in the scores for ease of use, perceived usefulness and attitude toward using between the two rounds. User experiences indicated a broad spectrum of views from joy from playing to annoyance. Suggestions for improvements given by participants were mainly about the barcode scanner as the scanner malfunctioned in round 1. Other technical improvements that were suggested were a lower frequency of push notifications, larger display buttons and preventing puzzles from causing the application to crash. Prior to the live walkthrough in stage 2, the application received a major update to incorporate further improvements such as instruction screens for all puzzles. During stage 2, eight DMARD users performed a walkthrough under supervision at the Sint Maartenskliniek. Four participants participated in stage 1 and four were new to the application. When seeing how users performed the various tasks, the app builders learned which steps were intuitive and which steps needed improvement. Overall, the design process led to valuable insights in patient acceptance, usability and suggestions for improvement. Consequently, the latest version of the application complied with the needs of end-users.

5. Programme implementation plan

Implementation was ensured by evoking intrinsic motivation of participants through addressing the following three needs: competence, autonomy and relatedness.[24,25,48] The complete puzzle environment consisted of three puzzle types – crossword, sudoku and wordsearch – with three levels of difficulty and at least 50 puzzles at each of these levels and 82 tangram puzzles across four themes: animals, letters, objects and humans.

To meet the need for *competence*, puzzles with increasing difficulty were available. Players could board a puzzle on the difficulty level they could master and develop skills by playing numerous puzzles in increasing difficulty. For players new to the game there was to option to get hints or help. The mastery of an individual was tracked by gaining experience points when playing puzzles and could view their progression level. Additionally, players could complete challenges such as 'find a word within 5 seconds after starting wordsearch' to be rewarded with badges allowing them to track and visualise their progress.

To meet the needs of *autonomy*, players had the freedom to choose which puzzle to play (individual choices were reflected in the badges collected) and the opportunity to solve a puzzle in multiple ways.

Finally, to meet the need of *relatedness* the world record 'playing crossword puzzles' was incorporated in the game. By playing crossword puzzles, each player contributed to breaking the world record crossword puzzles which was a group effort. Prior to starting a new crossword puzzle the individual's contribution to the world record and total progress was shown. To protect the privacy of the individual participants it was decided not to incorporate social interaction elements at this stage.

To further prevent drop-out we sought to balance triggers versus puzzles. Balance turned out to be: one trigger when starting the game and when opening a new puzzle after at least ten minutes of solving puzzles. Triggers appeared in random order to maintain variety in gameplay.

6. Evaluation plan

The intervention is currently being evaluated in a multi-centre randomised clinical trial: the GAMER study.[61] This study aims to examine the effect on medication adherence and clinical outcomes in patients with rheumatoid arthritis treated with DMARDs. A total of 220 patients will be randomised 1:1 to intervention or usual care and followed for three months. The intervention group will be instructed to install and play the puzzle game on their tablet or mobile phone. Playing the puzzle game is encouraged at the start of the study but otherwise completely voluntary. The main study parameter is adherence using the validated Compliance Questionnaire for Rheumatology (CQR)in an intention-to-treat analysis. Additionally, a pill count will be performed and the Beliefs About Medicine Questionnaire will be collected. Secondary clinical outcomes are the Health Assessment Questionnaire (HAQ) and the self-reported Rheumatoid Arthritis Disease Activity Index (RADAI). The CQR, BMQ, HAQ and RADAI have been proven valid and reliable in patients with rheumatoid arthritis.[32,33,65,66,34–38,62–64] Disease activity (DAS-28) [67,68] will be gathered if available. Lastly, the Technology Acceptance Model, as well-established model for evaluating usability of eHealth, will be applied to collect patient acceptance of the puzzle game. Data collection will be similar to stage 1 of the user-testing: the System Usability Score will assess ease of use, GameFlow will assess perceived usefulness, part of the uMARS will assess the attitude toward using and Google Analytics will collect actual use.[39–46]

Discussion

This paper describes the design rationale of a serious game aimed at improving medication adherence in RA. Our formative work with patients with RA in combination with the literature search and explorative study described above, led us to develop a mobile serious game as intervention. Focal points of this serious game were implicit medication attitudes, positivism and retention.

As Abraham et al. stated: development of serious games should detail on the extent of theoretical framework incorporated into game design and evaluate success by testing the player's retention of learning objectives.[69] This is why we chose to develop our intervention according to the IM framework whilst being guided by the Dual-Attitude Model and self-determination theory.[17,24] Even though the development was guided by the systematic IM framework, several choices still had to be made by the expert group. To ensure deliberate decisions we sought to incorporate many different areas of expertise among group members from clinical, to psychological and technical. Patients were not represented in the expert group but extensively consulted throughout the IM process: from the explorative study to elaborate user-testing.

The developed intervention did not contain medication taking (reminder) components, in contrast to other serious games aimed at improving medication adherence.[69] We decided not to incorporate the actual medication taking behaviour because we feared that this would be perceived as coercive and would lead to loss of retention because the act of medication taking would take playfulness and positivity out of the game.

The behaviour change techniques we have applied as medication-related triggers have not previously been tested to improve medication adherence. Even though there is no solid evidence for improving medication adherence, the extensive research on these techniques for stimulating healthy behaviour was considered a strong enough premise to apply these techniques in our serious gaming intervention.[21] Another reason for applying these behaviour change techniques was the fact that they have been successfully and effectively gamified.[26,27] It should be noted that the test conditions for these behaviour change techniques were generally well controlled: playing the gamified behaviour change techniques for a set period of time (at least for several minutes) without distractions. When applying these techniques in a mobile application as medication-related triggers, there is no control over the participants' setting which leads to variable exposure to the triggers. To ensure that the triggers were sufficiently dosed, participants need to be intrinsically motivated to play the game.

Whenever developing a serious game, a trade-off has to be made between the serious (i.e., the behaviour change techniques) and the game (i.e. the puzzles) which is why the usability testing is so important. The results from our usability testing indicated a positive response towards the app. However these findings were prone to selection bias and limited to patients willing to test the app. This type of testing, while appropriate for app development, may not reveal barriers to implementation in practice. The app was carefully designed to quickly engage users, sustain motivation for long-term app use and simultaneously apply behaviour change techniques. The success of these strategies will not be known until the app is tested in clinical practice.

To be considered effective, serious games must sustain their impact over the long-term and offer more than a short-term novelty effect.[69] The results of our evaluation study will hopefully answer if our serious game is successful in improving medication adherence.[61] If proven effective, additional studies should be performed to assess effectiveness on the longer-term (6 – 12 months) and to investigate the effective components more closely.

Conclusion

In conclusion, we systematically developed a serious game application to enhance adherence to DMARDs among patients with RA using the Intervention Mapping framework. Evaluation in a multi-centre randomised controlled trial will indicate whether the intervention is used and effective. This article could serve as a guideline for other healthcare providers when developing similar interventions.

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Conflicts of Interest

All authors declare no conflict of interest.

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Supplementary material S1. Triggers of serious puzzle game 'Medi & Seintje'

This document describes the five triggers employed by serious puzzle game 'Medi en Seintje'. These triggers are gamified behaviour change techniques. The serious game aimed to influence medication taking behaviour.

Multiple choice medication quiz

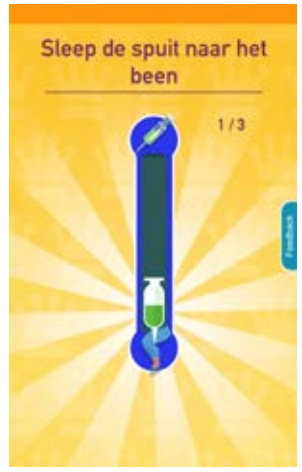
Domain Explicit cognition.
Strategy Reduce concerns by educating patients on how to best use DMARDs.
Based on education as means to improve medication adherence
Frequency Three questions per event
Description A set of multiple-choice questions was developed as an entertaining cognitive task to shift the necessity/ concern balance by educating on practical medicine information like how to best swallow a pill.

Dot-probe task

Domain Implicit cognition.
Strategy Adjust the automatic beliefs by strengthening positive associations. Part of the techniques applied are based on attention bias modification training.
Based on dot-probe
Frequency Two runs per event
Description On the screen icon character 'Medi' is shown standing between two empty squares. The instruction is to focus on icon character 'Medi' while a countdown from 3 to 1 is shown in the squares. After the countdown a stimulus is shown for 500 milliseconds in both squares after which the positive stimulus is replaced by an arrow pointing up or down while simultaneously a medication cabinet appears on the upper and lower part of the screen. The player is instructed to select the medication cabinet to which the arrow is pointing to find the medication. When the correct cabinet is selected, the medication jumps out.
Options Medication cabinet is either a regular cabinet or a refrigerator. Players are able to use a picture of their own medication.

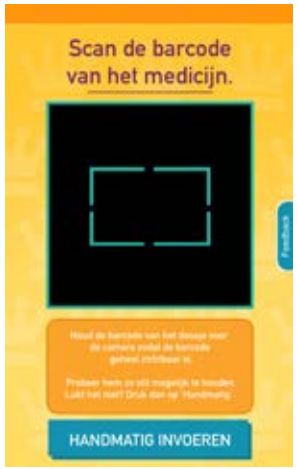
Visual search

Domain Implicit cognition and affect.
Strategy Adjust the automatic beliefs by strengthening positive associations. Part of the techniques applied are based on attention bias modification training. Adjust the valence of DMARD use by strengthening the positive associations through pairing DMARDs with a positive stimulus.
Based on visual search task: attention is drawn to medication (cognition) in an array of other positive stimuli (affect).
Frequency Three runs per event.
Description (Similar to reCAPTCHA) Players were tasked with finding medication in an array of six or nine pictures (all positive) within 10 seconds. If no or wrong input is given, the correct answers are shown after 10 seconds. The picture database consists of positive images (eg, the sun, smiling children) and rheumatological medication (eg, methotrexate blister, someone injecting a biological). The picture set could be supplemented with a picture of the player's medication.
Options Six or nine pictures shown. Single or multiple medication images. Players are able to use a picture of their own medication.



Slide to unlock

Domain Implicit affect.
Strategy Adjust the valence of anti-rheumatic drug use by strengthening the positive associations through pairing DMARDs with a positive stimulus.
Based on approach-avoidance task aimed at inducing approach or avoidance behaviour by simulating attraction and repulsion respectively
Frequency Three runs per event.
Description Players were instructed to swipe medication towards the bottom of the screen. The approach effect was stimulated by increasing the size along the way. At the bottom of the screen a picture starts to become clearer as the medication is drawn near. When the bottom is reached, the task is accomplished which was visualised by showering the medication in rays.
Options Either pill/mouth or syringe/leg combination. Players are able to use a picture of themselves.



Barcode scanner

Domain Implicit motivation.

Strategy Goal priming: passive, subtle, and unobtrusive activation by external stimuli such that people are not aware of the influence exerted by those stimuli.

Based on -

Frequency Once per event.

Description The barcode scanner literally motivated players to engage with the medication because the app would only unlock if a barcode of the medication was scanned. This feature was only active if the game had access to the camera. If medication was not at hand or failed to scan, players could manually enter the barcode.

Chapter 6

Gaming for Adherence to Medication using Ehealth in Rheumatoid arthritis (GAMER) study – a randomised controlled trial

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Abstract

Background
Patients' implicit attitudes towards medication need and concerns may influence their adherence. We developed a serious puzzle game that target these implicit attitudes by combining game-entertainment with medication-related triggers.

Objective
To examine the effect on adherence to disease modifying anti-rheumatic drugs (DMARDs) in participants with rheumatoid arthritis (RA) of a serious game that targeted implicit attitudes toward medication.

Methods
A multicentre randomised controlled trial (RCT) was performed with adults with RA that used DMARDs and possessed a smartphone/tablet. Control and intervention groups received care as usual. The intervention group played the serious game at will during 3 months. Game play data and online questionnaires Compliance Questionnaire on Rheumatology (CQR), Beliefs about Medicine Questionnaire (BMQ), Health Assessment Questionnaire (HAQ) and Rheumatoid Arthritis Disease Activity Index (RADAI) were collected. Primary outcome was DMARD implementation adherence operationalised as the difference in proportion of non-adherent participants (<80% taking adherence) between intervention and control group after 3 months using a Chi-squared test. Two sample t-tests and Wilcoxon rank-sum test were performed to test for differences on secondary outcomes.

Results
Of the 110 intervention participants that started the study, 87 participants (79%) installed the game and had a median playtime of 9.7 hours at 3 months. Overall, 186 participants completed the study. Adherence in intervention group (63%) and control group (54%) did not differ significantly (p=0.13) at 3 months. Neither were differences observed in CQR continuous score, beliefs about medication (BMQ) or clinical outcomes (HAQ and RADAI).

Conclusion
A serious game aimed at reinterpreting attitudes toward medication failed to show an effect on adherence to DMARDs or clinical outcomes in patients with RA. The game was played frequently indicating that it can be an effective channel for reaching patients.

Introduction

Disease Modifying Anti-Rheumatic Drugs (DMARDs) are effective in reducing disease activity and radiological progression and in increasing daily functioning in patients with rheumatoid arthritis (RA).[1,2] These benefits can only be achieved when patients adhere to the agreed pharmacotherapeutic regimen.[3] However around one third of patients with RA fail to correctly implement DMARD therapy in their daily routines, leading to suboptimal treatment effectiveness.[4–6] As a result there is a need for adherence improving interventions.

To date, interventions that aim to improve implementation adherence appear only partly effective.[7–10] Part of this ineffectiveness might be caused by interventions insufficiently targeting implicit behavioural factors of nonadherence. Behavioural intentions such as taking medication are the net result of a person's explicit (conscious) and implicit (unconscious) attitudes and these attitudes do not necessarily align.[11] Explicitly a person might say that medication alleviates symptoms whereas implicitly the same person regards medication as unnatural.[11,12] Habitual behaviour, like medication taking behaviour, happens mainly on an unconscious level where implicit attitudes dominate.[13] An effective strategy to improve medication adherence might thus be to target implicit attitudes.[14]

Implicit attitudes are readjusted by training the brain to interpret a stimulus differently and consequently change nonconscious processes.[15] This could for instance be done by performing behavioural tasks that lead to attending to a neutral or positive stimulus when confronted with a cue, which in our case would be medication.[16] Such training needs rigorous and repetitive performing of behavioural tasks to change nonconscious processes and eventually behaviour. eHealth can be a suitable mode of delivery for repetitive practicing as it is easily accessible and allows patients to perform tasks at a convenient place and time. Repetitive practicing requires ongoing engagement with the intervention that is best achieved when participants are intrinsically motivated. Intrinsic motivation can be elicited by serious games: games that intend to entertain and to achieve at least one additional goal simultaneously such as learning or health.[17] Serious games have been shown to positively influence eating behaviour by targeting implicit attitudes in children.[18] No games have, as yet, been developed to counter suboptimal long-term medication adherence by targeting implicit attitudes in adults.

We developed a serious puzzle game aimed at improving medication adherence by targeting implicit attitudes toward medication in patients with RA.[19] The serious game was built as an application on smartphone or tablet and contains four puzzle types: crossword, sudoku, word search and tangram. When opening the game or a puzzle, players had to perform behavioural tasks that aimed at reinterpreting their attitudes toward medication. The Gaming for Adherence to Medication using Ehealth in Rheumatoid arthritis (GAMER) trial aims to assess the effectiveness of this serious game on the implementation adherence of DMARDs compared to usual care alone.

Methods

Trial design and setting

This is a multi-centre randomised assessor-blinded controlled trial with a follow-up of three months. The trial has been registered in the Dutch trial register under NL7217 (https://www.trialregister.nl/trial/7217) and reporting adheres to both the CONSORT-EHEALTH and EMERGE guideline. Ethical approval was asked for and waived by the local Medical Research Ethics Committee of the Radboud university medical centre (METC Oost Nederland, protocol number 2018-4648) and the trial complies with the Helsinki declaration. Two patient research partners were involved in the design phase of the study and another two patient research partners discussed the results and its implications with one of the researchers (BP). The GAMER trial was conducted in the outpatient rheumatology clinics of six hospitals in The Netherlands between August 2019 and April 2021.

Recruitment and eligibility criteria

The hospital information system provided a list of eligible participants who were randomly selected by using a random number generator and were sent an information letter with informed consent form and a reminder after no response by 3 weeks. For participants, the goal of the study was framed as assessing the effect of playing a puzzle game on the experience of RA disease burden. Medication adherence was not mentioned to prevent participants from modifying their adherence behaviour.

Inclusion criteria were: clinical diagnosis of RA, current DMARD use (no adherence criteria), self-management of medication (no support of caregiver, home care or use of a multi-dose drug dispensing system), possession of a smartphone or tablet running on iOS/Android software and a valid email address. Participants were excluded if they were not proficient in the Dutch language or participated in another trial. After providing written informed consent, participants were telephoned by the research team to check if they were compliant with eligibility criteria.

Randomisation and blinding

Participants were allocated to the intervention or control group on a 1:1 ratio. Randomisation was concealed before allocation and performed by CastorEDC, stratified by hospital and variable block randomisation with block sizes of two, four and six. Due to the design of the trial, blinding of participants and researchers was not possible although the assessor was blinded. Caregivers were not informed of study allocation.

Study arms

Control group

The control group received care as usual only. This consisted of regular consultations with the rheumatologist and is detailed in the treating guideline of the Dutch Rheumatology Association.[20] Implementation adherence is subject of the consultation only if problems arise or if there are reasons to believe there is nonadherence. Control group participants were offered access to the intervention when they finished the final questionnaire at three months.

Intervention group

Intervention participants also received care as usual. Next to this they received email instructions to download and install the serious game free of charge using their research code and were reminded to do so twice. Participants were told to play the intervention at will. If participants allowed app notifications, they received a daily 'come-and-play' reminder.

The development and participant pilot-testing of the serious game was guided by the Intervention Mapping framework and published elsewhere [19]. Game Solutions Lab developed the game in co-creation with the Sint Maartenskliniek and AbbVie. In short, the storyboard of the serious game consisted of two 'hosts': a cartoon tablet and capsule. They gave puzzle instructions, encouragements and daily 'come-and-play' notifications if these were allowed in the game's settings. The 'game' part contained four puzzle types: crossword, sudoku, word search and tangram. Each puzzle type had varying difficulty levels and at least 50 puzzles to play. The 'serious' part consisted of behavioural tasks that players had to perform to open the game or a puzzle. The behavioural tasks aimed to target implicit attitudes toward medication and were gamified behaviour change techniques based on attention bias modification, evaluative conditioning and goal priming.

Technical issues were resolved during the trial but content and functionality of the app remained unaltered. During the trial one technical error occurred where the app failed to communicate with the server. Forty-one participants were possibly hindered by this error and informed by email how to resolve the issue.

Data collection

Participants received a study code and all data were logged using electronic data management software CastorEDC (ISO 27001 and ISO 9001 compliant). CastorEDC was also used to send questionnaires through email. Medication adherence and beliefs about medication questionnaires were collected at baseline, one and three months. In addition clinical patient-reported outcomes were collected at three months, intervention play data at one and three months and demographic data and gaming experience at baseline.

When the study commenced on August 2019, participants were telephoned to make a start-of-study appointment in the pharmacy to allow for a pill/syringe count. Due to the COVID-19 regulations effective from March 2020 (leading to pharmacies delivering medication) pill/syringe count was abandoned and the study became fully digital.

Measurement instruments

Medication adherence

Primary outcome was DMARD implementation adherence at three months, assessed as the difference in proportion of non-adherent participants (<80% taking adherence 3) between intervention (serious game and usual care) and control group (usual care) using the discriminant function of the Compliance Questionnaire on Rheumatology (CQR, 19 Likert-scaled items, item scores ranging from 1 to 4 [21]). The negative formulated items were recoded after which the critical cut-off score of -0.5849 was calculated to discriminate between adherent (≥80%) and non-adherent (<80%) as described by De Klerk et al.[22] The discriminant function is able to detect whether a patient is adherent with a sensitivity of 62% and a specificity of 95% as validated using an electronic medication monitoring device over a period

of six months.[22] Because it was uncertain if participants would engage with the game for three months, the effect of the intervention on medication adherence was also assessed at one month using the CQR. Additionally, we report on the continuous CQR score which was calculated by transforming sum scores to a scale between 0 and 100.[21]

Medication adherence was also assessed using pill/syringe count. Participants were supplied with a set and surplus amount of one of their DMARDs at study start and asked to commit to using this stock only during the study. At the end of the study participants brought the remainder to the pharmacy and the pharmacy technician counted the medication in presence of the participant. This outcome was abandoned in March 2020 when Dutch COVID-19 regulations took effect.

Beliefs about Medication

The Beliefs about Medicine Questionnaire Specific (BMQ-Specific, 10 Likert-scale items, item scores ranging from 1 to 5 [23,24]) which assesses both beliefs about the necessity of medication and concerns about medication was also completed at one and three months. The sum scale score for necessity beliefs was subtracted from the sum scale score for concern beliefs to yield the necessity–concerns differential (NCD) score (range: -20 – 20). A positive NCD score indicates that necessity beliefs dominate concern beliefs.

Clinical outcomes

To assess the effect of the intervention on clinical outcomes, the Rheumatoid Arthritis Disease Activity Index (RADAI, 5 items) and the Health Assessment Questionnaire (HAQ, 20 items with 5 dimensions) were collected at three months. The patient-reported disease activity using RADAI correlated with physician's assessment and swollen joint count (Spearman's $\rho = 0.54$, $P < 0.01$ for both) and changes in the RADAI correlate strongly ($r2 = 0.70$, $P < 0.0001$) with changes in the Disease Activity Score-28 (DAS28, the golden standard for clinical disease activity in rheumatoid arthritis). As such, the RADAI is deemed a highly reliable and valid self-administered measure of disease activity. All 5 items are transformed into a zero to ten scale and averaged to provide a single 0 - 10 index of patient-assessed disease activity where a higher score indicates higher disease activity. The HAQ provides a single index value for health status with good reliability ($\alpha = 0.88$). This disability index (HAQ-DI) is determined by the highest subcategory score for each category unless aids or devices were used. Participants were included in this calculation only if at least six of the eight categories were completed. The HAQ-DI (range: 0–3) is the average of these eight category scores with higher scores indicating more disability (category 0–1: mild to moderate disability, 1–2: moderate to severe disability, 2–3: severe to very severe disability).

Intervention use

Intervention use was determined by extracting the following statistics from Google Firebase: total play time, number of sessions, average session time, number of completed behavioural tasks and the time span in which activity was observed. Additionally, acceptability of playing the serious game was assessed according to the Technology Acceptance Model (TAM).[25] Methods and results are available as Supplementary Material Data S1.

Sample size

Previous studies in the Sint Maartenskliniek demonstrated that 35% of patients with RA that use DMARDs are non-adherent.[26,27] A slight Hawthorne effect was expected for all participants due to actively measuring adherence, meaning that nonadherence was expected to decrease to 30% of the population irrespective of randomisation. With an assumed intervention effect of 50% on non-adherent participants (without effecting adherent participants allowing for one-sided testing), the hypothesis was that 15% of the intervention group would be nonadherent compared to 30% in the control group at three months. A target sample size of 110 participants per arm was computed to provide 80% power to detect a single-sided 15% difference in adherence after three months with 15% loss to follow-up.

Statistical analysis

Descriptive statistics were performed to describe patient and disease characteristics.

Primary end-point of the study, adherence at three months using the discriminant function of the CQR, was assessed with a Chi-square test to test for difference in proportions between study groups. Two sample t-tests and Wilcoxon rank-sum test were performed to test for differences between study groups for normally distributed and non-normally distributed variables, respectively. Primary analyses were performed according to the intention-to-treat principle (ITT). Secondary analyses included a per-protocol analysis where all intervention participants who played the game for more than one hour during the study period were considered adherent to the protocol. Exposure-response analyses were also performed: total play time was plotted against the continuous outcomes (CQR, BMQ NCD, RADAI and HAQ) to determine regression coefficient. In addition playtime was plotted for both adherent and non-adherent intervention participants, based on the CQR, to determine whether there was a difference in average playtime between both groups.

P-values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata version 13.1.

Results

Participants

A total of 2,026 eligible participants were invited for participation which led to 111 participants starting the study in the control group and 110 participants in the intervention group (see figure 1). Apart from more males being lost to follow-up in the intervention group, there were no differences between study population and dropouts (data not shown). As 15 participants did not play the intervention for more than one hour, they were excluded per-protocol leaving 70 participants for analysis.

Participant's mean age was 61 years (SD 12) with the majority being female (73%) and living together (81%) (see table 1). Participants had RA for a median duration of 10 years and 67% were RF/ACPA positive. At baseline, 38 participants in the control group (35%) and 43 participants in the intervention group (39%) were non-adherent.

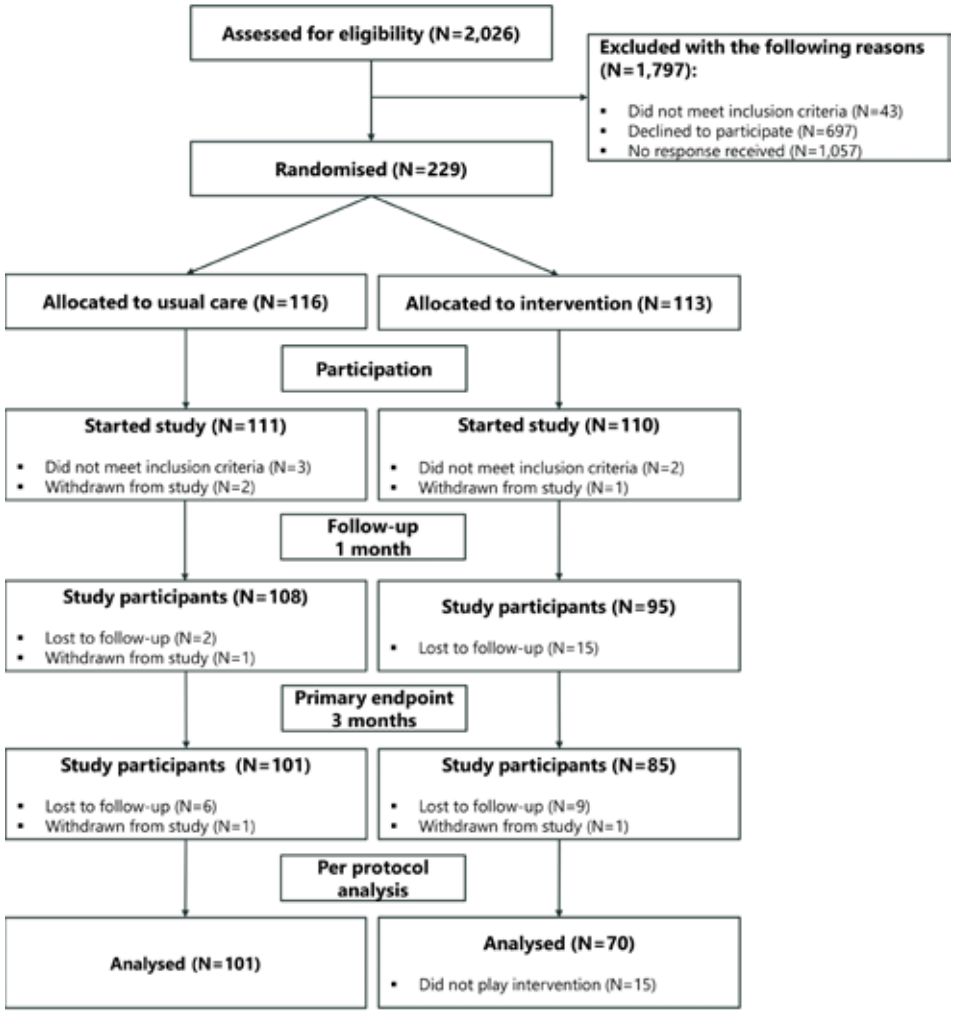


Figure 1. Flowchart of GAMER study participation

Table 1. Baseline characteristics of participants in control and intervention group

	Control *(N=111)**	Intervention *(N=110)**
Age in years (mean ± SD)	61 ± 12	61 ± 12
Female (N (%))	78 (70)	84 (76)
Living situation (N (%))		
Alone	22 (20)	20 (18)
With partner and/or children	88 (80)	90 (82)
Educational level (N (%))		
Low	11 (10)	20 (18)
Middle	52 (47)	45 (41)
High	46 (41)	45 (41)
Frequency of playing games (N (%))		
Never to once a month	31 (28)	31 (28)
Once to multiple times a week	41 (37)	36 (33)
Once to multiple times a day	38 (34)	43 (39)
Disease duration in years (median [IQR])	10 [4 – 17]	9 [4 – 15]
RF/ACPA positive (N (%))	77 (69)	70 (64)
Current DMARD use (N (%))		
1	52 (47)	62 (56)
2	50 (45)	39 (35)
≥3	9 (8)	9 (8)
Nonadherent according to CQR (N (%))	38 (35)	43 (39)
BMQ-Specific NCD score (mean ± SD)	5.8 ± 4.3	5.0 ± 5.1

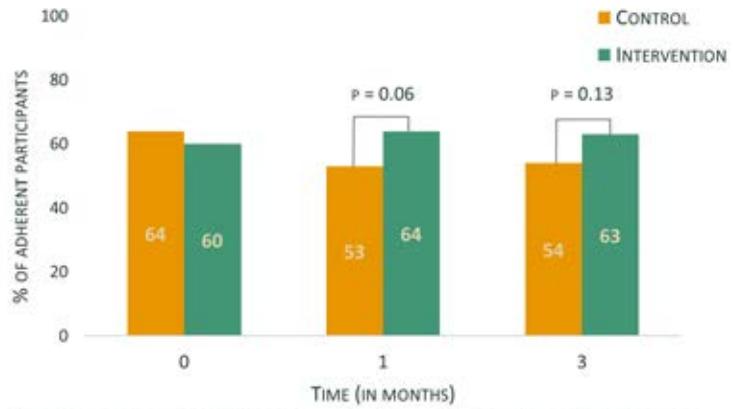
Abbreviations: SD – standard deviation; N – number; IQR – inter quartile range; RF/ACPA – rheumatoid factor/anti-citrullinated protein antibody; DMARD – disease-modifying anti-rheumatic drugs; CQR – Compliance Questionnaire on Rheumatology; BMQ – Beliefs about Medication questionnaire * Some categories do not add up to 100% due to missing data.

Primary outcome

At three months 63% of the intervention participants were adherent compared to 54% of the control group (see figure 2). This difference was not statistically significant (p = 0.13). The difference in percentage of adherent participants was slightly larger at one month (64% vs 53%; p = 0.06) but the difference remained statistically non-significant.

Secondary outcomes

The serious game did not show an effect on secondary medication outcomes at three months (see table 2). Medication adherence as measured using the objective pill count was higher in the total population (mean adherence around 95%) when compared to the proportion of adherent participants according to the subjective CQR self-report. Self-reported medication outcomes at one month were comparable (data not shown). The serious game intervention failed to show an effect on self-reported secondary clinical outcomes as well (see table 2).



Proportion of adherent participants as determined by the Compliance Questionnaire on Rheumatology (CQR) at baseline, 1 month and 3 months for control and intervention group.

Figure 2. Medication adherence rates for control and intervention group over time

Table 2. Study outcomes at end-point (3 months)

	Control group (N=101)	*Intervention group (N=85)*	*Group difference [95% CI]*
Primary outcome			
Adherent (N (%))*	55 (54)	52 (63)	-8% [-22 – 6]
Secondary medication outcomes			
CQR continuous (mean ± SD)	75 ± 12	73 ± 11	2.2 [-1.1 – 5.5]
Pill count# (mean ± SD)	95 ± 16	97 ± 8	-2.3% [-9.7 – 5.1]
BMQ-Specific NCD score (mean ± SD)	4.8 ± 4.2	5.3 ± 4.7	-0.5 [-1.8 – 0.8]
Secondary clinical outcomes			
RADAI score (median [IQR])	2.5 [1.2 – 4.0]	2.5 [1.5 – 4.2]	0.0 [-0.8 – 0.8]
HAQ score (median [IQR])	0.8 [0.3 – 1.4]	0.6 [0.3 – 1.4]	-0.1 [-0.5 – 0.2]

Abbreviations: 95% CI – 95% confidence interval; n – number; SD – standard deviation; CQR – Compliance Questionnaire on Rheumatology; BMQ NCD – Beliefs about Medication questionnaire necessity-concerns differential; RADAI – Rheumatoid Arthritis Disease Activity Index; HAQ – Health Assessment Questionnaire; IQR – interquartile range. * Percentage of the total number of participants excluding missing data. # N=21 for the control group and N=24 for the intervention group.

Serious game play data

Of the 110 intervention participants that started the study, 87 participants (79%) installed the game. These participants had a median playtime of 6.2 hours at one month and 9.7 hours at three months (see Table 3). Average session time was approximately 25 minutes throughout the study and the median number of sessions increased from 16 at one month to 36 at three months. During play, participants completed a median of 20 behavioural tasks at one month and 46 at three months. 75% (64) of the participants that installed the game was active for

at least 30 days out of 90. Due to a communication error with Google Firebase there were no user data between 6-1-2020 and 24-2-2020. As a result the data of seven participants were incomplete.

Per-protocol and exposure-response analyses

Per-protocol analyses did not differ from the ITT analyses on primary and secondary outcomes. No exposure-response effect was found on any of the outcomes (results not shown).

Table 3. Serious game play data at 1 and 3 months

Actual use	*1 month (N=86)**	*3 months (N=78)‡*
Play time in hours (median [IQR])	6.2 [2.3 – 11.9]	9.7 [3.3 – 24.3]
Number of sessions (median [IQR])	17 [6 – 36]	36 [11 – 78]
Session time in minutes (mean ± SD)	25 ± 15	23 ± 15
Completed behavioural tasks (median [IQR])	20 [7 – 50]	46 [13 – 115]
Active time span [maximum of 90 days] (median [IQR])		79 [30 – 90]#

Abbreviations: N – number; IQR – interquartile range; SD – standard deviation. * Data of one player is missing at 1 month due to a communication error with Google Firebase. ‡ *N=78 because 8 participants played the serious game but did not respond to the study questionnaires at month 3. N=70 for the per protocol analysis on the primary outcome (see figure 2).* # N = 86

Discussion

This multicentre randomised controlled trial evaluated the effect of a serious game at improving implementation adherence of DMARDs. It showed that the serious game was frequently played but did not lead to improved medication adherence or clinical outcomes at three months.

Comparison with similar interventions is difficult because there have been limited studies on serious games aimed at enhancing medication adherence. In addition, there is great heterogeneity in intervention approach, study design and medication adherence assessment. Previous studies mainly describe development and testing of serious games that either gamify adherence behaviour by rewarding medication intake or indirectly promote medication adherence through education.[28,29] Both effect on medication adherence and medication knowledge is modest and inconsistent.[28,29] Apart from serious games, evidence on other interactive eHealth interventions for improving medication adherence is more abundant. A recent systematic review showed interactive eHealth interventions can be effective in improving medication adherence especially when channelled through Short Messaging Service, Interactive Voice Response, calls or mobile apps.[30] This illustrates eHealth can be a suitable channel for improving medication adherence but application of serious games needs further development.

Two aspects of the intervention will be discussed that could possibly relate to the lack of effect: behavioural task effectiveness and the absence of integration in care. First, targeting implicit attitudes using eHealth has shown to be effective in changing health behaviour [16,18] but has not been applied to medication taking behaviour. Several reasons can be given for this: i) the behavioural tasks are not effective in changing implicit medication attitudes, ii) changing implicit medication attitudes does not automatically lead to improved medication adherence, iii) patients with longstanding RA are less susceptive to changing implicit medication attitudes (median disease duration was 10 years in our study) and iv) there was insufficient or infrequent exposure to the behavioural tasks as exposure has shown to be a significant moderator of behaviour change technique effectiveness.[16] Second, the serious game was not integrated in the RA care pathway and operated independently of the care context. Research showed that combining the eHealth intervention with healthcare professional interaction increases the chances of intervention effectiveness.[31,32] The GAMER study refrained from integrating the serious game in the care pathway because it was expected to be at the expense of feasibility.
Besides the beforementioned intervention restraints, study methodology may also explain the negative outcomes of our trial. Medication adherence is difficult to determine and it is therefore advised to combine subjective and objective measures.[33] Although full comparison of both measures in our study was not possible due to missing pill count data, CQR discriminant function and pill count (with a cut-off at 80%) aligned in only 50% of the cases (data not shown). The self-reported CQR is easier to collect but might underestimate true adherence. In addition, the study population could have been ill matched with the intervention's target population because a large proportion of participants were adherent and/or had no negative implicit attitudes about DMARDs. Adherence was no criteria for inclusion in order to reflect clinical practice and measuring implicit attitude using implicit association tests was deemed too high a participant burden. As a result, the intervention target (i.e. implicit attitudes) was not assessed as a study outcome which is a flaw of this study

The intervention was channelled as a serious mobile game because the smartphone is omnipresent in patient's everyday life. As a result, game retention was high (median voluntary playtime of 9.7 hours at three months) and comparable to serious games where participants were encouraged to play.[34,35] This channel therefore appears to be effective in reaching the patient but, our serious game only reached part of the population with a response rate of 11% for the GAMER study. Of note, participants were only invited by a posted information letter with a reminder letter if they had not responded within four weeks. Our experience is that such low intensity recruitment strategy generally leads to a participation rate of 20 to 30%.[36]

To increase the chances of intervention effectiveness, future endeavours should explore integration of the serious game in the care pathway. Additionally, the behavioural tasks should be further investigated to determine the most effective behavioural tasks and corresponding dose intensity. When investigating the effects of the adjustments the trial design should fit the rapidly evolving nature of eHealth to prevent the intervention from being static over longer periods of time, for example using a trials within cohorts (TWICS) design where a cohort is continuously measured and for each design cycle, a new random participant sample is offered the intervention and outcomes compared between the sample and the cohort.[37]

Conclusion

In conclusion, our serious game aimed at encouraging a positive attitude towards DMARDs failed to show an effect on adherence to DMARDs or clinical outcomes in patients with RA. The serious game was played frequently indicating that it can be an effective channel for reaching patients.

Acknowledgements
Game Solutions Lab developed the game in co-creation with the Sint Maartenskliniek and AbbVie Inc. We thank all patients who participated in our study. We also thank Willemijn van Sterkenburg for her help in conducting the trial and Katrina Go for her help in the data analysis.

Conflicts of Interest
B. Pouls, C. Bekker, F. Gundogan, R. Hebing, H. van Onzenoort, L. van de Ven, R. Tieben , J. Vriezekolk and S. van Dulmen have no conflicts of interest to report. H. Vonkeman reports grants and/or personal fees from AbbVie, Amgen, AstraZeneca, BMS, Celgene, Celltrion, Galapagos, Gilead, GSK, Janssen-Cilag, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi-Genzyme, UCB all outside the submitted work. J. Vriezekolk reports speaker fees from Eli Lilly and Galapagos all outside the submitted work. B. van den Bemt reports grants and/or personal fees from UCB, Pfizer, Sanofi-Aventis, Galapagos, Amgen en Eli Lilly all outside the submitted work.

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Supplementary material S1. Data on the technology acceptance of serious game 'Medi en Seintje'

Methods

Measurement instruments

Technology Acceptance

Acceptability of playing the serious game was based on all intervention participants who installed the game. Acceptability was determined using the Technology Acceptance Model [TAM].[1] This model postulates that ease of using a technology influences the perceived usefulness and the attitude toward using and together form the behavioural intention to use a technology which leads to actual use. Ease of use was measured using the System Usability Score [SUS, 10 Likert-scale items, item scores ranging from 1 to 5] questionnaire taken directly from the TAM.[1] Answers are transformed to a score between 0 and 100.[2] The SUS score is highly reliable [alpha = 0.91] and useful over a wide range of interface types.[3] Perceived usefulness of the game was operationalised as enjoyment and assessed using the playful experiences questionnaire [PLEXQ, 17 constructs of playfulness, each measured through three items].[4] The constructs nurture, fellowship, cruelty and subversion were removed as these did not align with the intention of the serious puzzle game. Constructs are taken together to distinguish a four-factor structure of playfulness: stimulative, pragmatic, momentary and negative experiences.[4] Perceived usefulness of the behavioural tasks was assessed at three months with five statements on a five-point Likert scale (ranked 0 – 4).

Secondary analyses

Secondary analyses included results at one month and a per-protocol analysis where all intervention participants who played the game for more than one hour during the study period were considered adherent to the protocol. Exposure-response analyses were also performed: total play time was plotted against the continuous outcomes (CQR, BMQ NCD, RADAI and HAQ) to determine regression coefficient. In addition, playtime was plotted for both adherent and non-adherent intervention participants, based on the CQR, to determine whether there was a difference in average playtime between both groups.

P-values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata version 13.1.

Results

Acceptability of the serious game

Ease of use was scored an average of 66 out of 100 during the study. According to the adjective rating scale of Bangor et al.[3], this means usability can be regarded as 'good' [see Table S1].

Perceived usefulness of the game was considered to be the playfulness experiences of the serious game. Experiences did not differ much over the study and had an overall mean score of around 3 out of 5 with the exception of the negative experiences which scored around 2. Patients scored neutral to negative on the statements regarding the behavioural tasks.

Table S1. Acceptability outcomes of the serious game at 1 and 3 months

	1 month (n=86)	*3 months (n=78)*
Ease of use		
Average SUS score (0-100) *mean ± SD*	66 ± 16	66 ± 14
Perceived usefulness of the game		
Stimulative experience (1-5)	3.2 [2.8 – 3.5]	3.2 [2.6 – 3.6]
Pragmatic experience (1-5)	3.0 [2.7 – 3.4]	2.9 [2.6 – 3.2]
Momentary experience (1-5)	3.0 [2.6 – 3.4]	2.9 [2.6 – 3.3]
Negative experience (1-5)	2.3 [1.7 – 2.7]	2.0 [1.7 – 2.7]
Perceived usefulness of the behavioural tasks		
It was clear to me that the behavioural tasks were meant to remind me of my medication. (0-4)	3 [2 – 3]	
I find it agreeable to be reminded of my medication through performing a behavioural task. (0-4)	1 [1 – 2]	
Performing a behavioural task helps me in using my medication. (0-4)	1 [0 – 1]	
The push notifications reminding me to come and play were of great added value. (0-4)	1 [1 – 2]	
The serious puzzle game is of added value in the treatment of my rheumatoid arthritis. (0-4)	1 [0 – 2]	

Abbreviations: IQR – inter quartile range; no. – number; SD – standard deviation.
All outcomes are median plus interquartile range unless otherwise stated.

Study outcomes at one month

At one month 64% of the intervention participants were adherent compared to 53% of the control group and 95% confidence interval of the difference was -22% to 6% and not statistically significant (see Table S2).

The serious game did not show an effect on secondary medication outcomes at one month (see Table S2). Results were similar to the outcomes at three months (see Table 2 in the manuscript).

Table S2. Study outcomes at one month

Outcome	*Control group (N=108)*	*Intervention group (N=95)*	*Group difference [95% CI]*
Adherent (N, %)*	56 (53)	59 (64)	-8% [-22 – 6]
CQR continuous (mean, SD)	74 ± 11	74 ± 11	0.4 [-2.8 – 3.6]
BMQ-Specific NCD score (mean, SD)	5.3 ± 4.5	4.8 ± 4.7	-0.5 [-1.8 – 0.8]

Abbreviations: 95% CI – 95% confidence interval; n – number; SD – standard deviation; CQR – Compliance Questionnaire on Rheumatology; BMQ – Beliefs about Medication questionnaire.
* Percentage of the total number of participants excluding missing data.

Per protocol analysis

Of the 110 intervention participants that started the study, 87 participants (79%) installed the game and 70 participants (75%) played the game for at least an hour and were eligible for the per protocol analysis.

The per protocol analysis showed no differences between control and intervention group on medication or clinical outcomes (see Table S2). Pill count adherence was much higher (around 96%) as compared to adherence scored by the Compliance Questionnaire on Rheumatology (around 50%).

Table S3. Per protocol analysis on medication outcomes at three months

	Control group (N=101)	*Intervention group (N=70)*	*Group difference [95% CI]*
Medication outcomes			
Adherent (N, %)*	55 (54)	42 (62)	-7% [-22 – 8]
CQR continuous (mean, SD)	75 ± 12	72 ± 11	2.9 [-0.6 – 6.4]
Pill count# (mean, SD)	95 ± 16	97 ± 9	-2.0% [-9.7 – 5.7]
BMQ-Specific NCD score (mean, SD)	4.8 ± 4.2	5.3 ± 4.7	-0.5 [-1.9 – 0.8]
Clinical outcomes			
RADAI score (median, IQR)	2.5 [1.2 – 4.0]	2.5 [1.5 – 4.1]	0.0 [-0.9 – 0.8]
HAQ score (median, IQR)	0.8 [0.3 – 1.4]	0.6 [0.3 – 1.4]	-0.1 [-0.5 – 0.2]

Abbreviations: 95% CI – 95% confidence interval; n – number; SD – standard deviation; CQR – Compliance Questionnaire on Rheumatology; BMQ NCD – Beliefs about Medication questionnaire necessity-concerns differential; RADAI – Rheumatoid Arthritis Disease Activity Index; HAQ – Health Assessment Questionnaire; IQR – interquartile range. * Percentage of the total number of participants excluding missing data. # N=21 for the control group and N=22 for the intervention group

Exposure-response analyses

Playtime of intervention participants was plotted against continuous outcomes CQR (figure S1), BMQ NCD (figure S2) and HAQ and RADAI (figure S3) and regression coefficients were fitted. None of the continuous outcomes showed a relation with playtime. Playtime was also plotted in a boxplot for both nonadherent and adherent intervention participants as categorised by the CQR (figure S4). Median playtime and interquartile range do not differ between nonadherent and adherent participants. Both exposure-response analyses showed there is no relation between playtime and study outcomes.

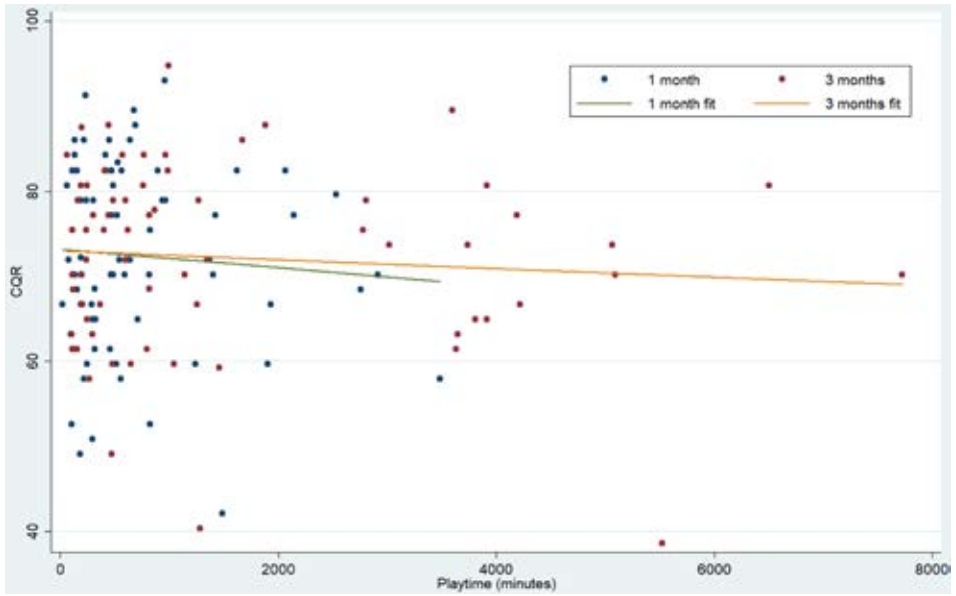

Figure S1. CQR continuous score versus playtime and plotted regression line at 1 and 3 months

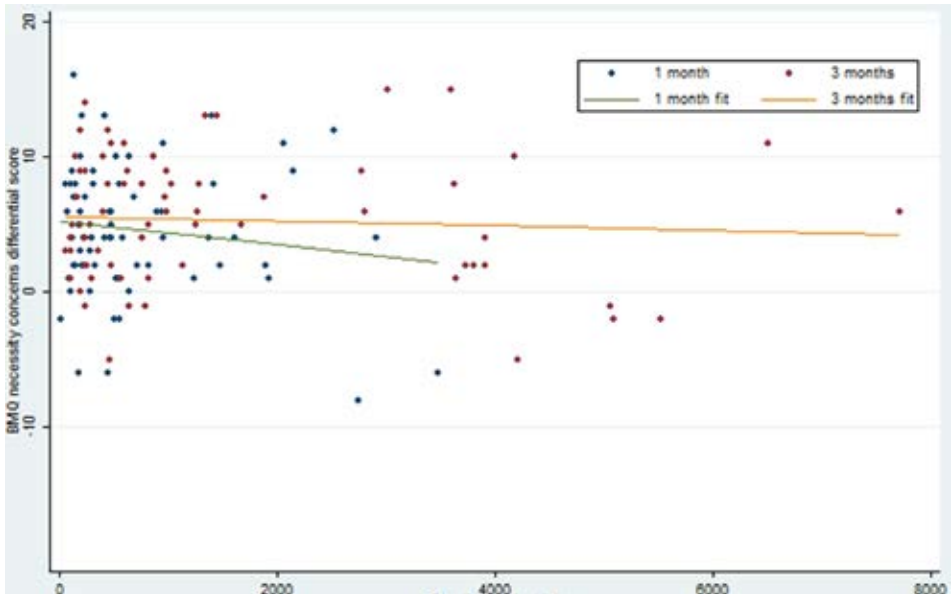

Figure S2. BMQ NCD-score versus playtime and plotted regression line at 1 and 3 months

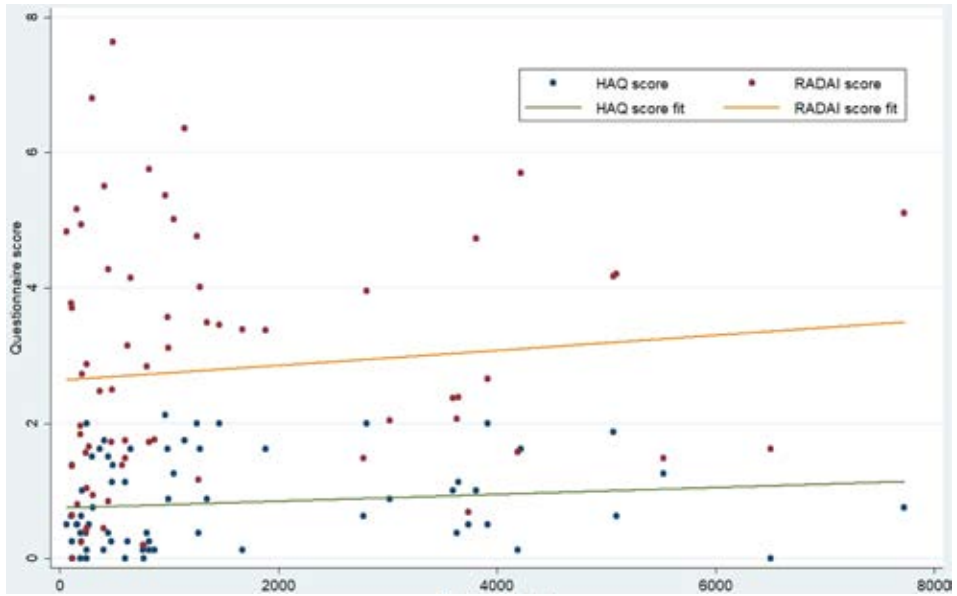

Figure S3. HAQ and RADAI score versus playtime and plotted regression line at 3 months

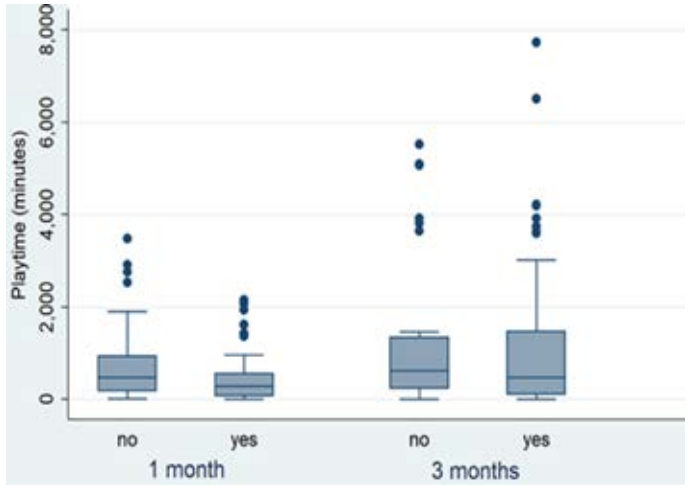

Figure S4. Boxplots of playtime for nonadherent (no) and adherent (yes) intervention participants at 1 and 3 months

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Chapter 7

General discussion

Aim of this discussion

This thesis investigated how eHealth interventions are experienced by patients and whether these eHealth interventions benefit patients' medication management in rheumatology. In this thesis three eHealth interventions – an electronic injection device (**Chapter 2**), a gout flare query application (**Chapter 3**) and a serious puzzle game (**Chapter 5 & 6**) – were test cases in patients with inflammatory rheumatic diseases as model for other long-term conditions where medication is the main treatment. This discussion aims to put the findings of this thesis in perspective and will be guided by three questions:

- How can eHealth help solve problems related to patients' medication management?
- Can all patients benefit from eHealth?
- How can eHealth interventions in support of patients be sustained?

How can eHealth help solve problems related to patients' medication management?

Answer to this question will start with a short introduction to this thesis's objective, a summary of our main findings and finally effectiveness of eHealth on drug related problems will be discussed. Drug-related problems such as medication nonadherence and erroneous medication use occur frequently in patients using long-term medication.[1–5] Frequency and incidence is expected to increase as the population ages and polypharmacy increases. Moreover, patients generally use long-term medication at home on a daily or weekly basis and visit healthcare providers for control consultations once to four times a year. Incorrect use of long-term medication happens out of sight of healthcare providers making it hard to provide support at the right time. Consequently, there is a need for ways to provide continuous support accessible by patients wherever they are. In the current healthcare system this would mean a major increase in healthcare demand whereas it is estimated that the healthcare workforce will not keep up with increased healthcare demand.[6] As a result, healthcare providers will lack time and resources to support patients in managing their medication. eHealth can be a possible solution if it can reduce drug-related problems and/or provide medication management support more efficiently as time and location independent medium.[7–9]

In this thesis we showed eHealth has the potential to reduce drug-related problems in patients with inflammatory rheumatic diseases. Patient experiences with medication use can be improved by providing patients with an electronic injection device (**Chapter 2**) and eHealth interventions can improve adherence to long-term medication (**Chapter 4**). This systematic review showed simple interventions such as SMS reminders and brief telephone calls can improve medication adherence. The gout app we developed could be deployed in patients with established gout to proactively provide care during a gout flare (**Chapter 3**). The serious game we developed was played frequently but not effective in improving medication adherence (**Chapter 6**). Other research on eHealth interventions showed eHealth can improve self-management of diabetes, hypertension and HIV.[10–12] These studies also stress eHealth is not always effective: some effects are only short term, some effects are only established by a combination of interventions and some affect only part of the desired behaviour. The above shows effectiveness of eHealth can be further improved.

Improving effectiveness of eHealth interventions might be achieved by tailoring the intervention to patient needs. In concrete terms this means assessing the patient's problem/

preferences and then selecting a solution that fits both problem and patient. This might sound obvious but drug-related problems can take on many forms and can occur throughout pharmacological treatment making it harder to apply the right intervention at the right time. Besides, interventions are frequently applied to all patients in clinical practice ("the one-size fits all" approach). Similarly, we applied our serious game to all patients with rheumatoid arthritis as both adherent and nonadherent patients were eligible to participate in our GAMER study (**Chapter 6**). However, with part of the population being adherent, there was a smaller chance to show serious game effectiveness on medication adherence. Tailoring the serious game to non-adherent patients would have increased chances of showing effectiveness but performing adherence screening would decrease clinical application. Thus, tailoring the intervention to patient needs is a balancing act between screening for the right patients and clinical feasibility of this screening. Research can also inform on the clinical feasibility of eHealth interventions as we showed in the gout app feasibility study (**Chapter 3**). We performed this trial in both patients with suspected and established gout and learned that tele-monitoring could be deployed unaltered in patients with established gout but needed alterations in patients suspected for gout such as less frequent querying.

Effectiveness of eHealth interventions extends beyond reducing drug-related problems and eHealth can also provide medication management support more efficiently as eHealth provision is independent of time and space.[8,9] For example, eHealth can offer continuous monitoring for patients by logging disease activity or medication outcomes (e.g. adverse effects or biomarkers) on a daily basis or it can increase access to healthcare by providing healthcare from home. The latter example is the reason eHealth surged during the COVID-19 pandemic as video consultations allowed usual care to take place during COVID-19. For eHealth to be considered effective, it should either improve clinical outcomes or make healthcare more efficient and preferably both. This is illustrated by Ebbens et al. who showed medication reconciliation via an online patient portal is non-inferior to medication reconciliation by a pharmacy technician and subsequently could save about three minutes per patient.[13] An additional four minutes could be saved if eHealth applications functioned optimally and allowed automatic data transfer.[13] Important to notice is that although authors speak of time saved time investment was actually shifted from healthcare provider to patient or caregiver. In order for eHealth to optimally help solve problems related to patients' medication management, it should save time and/or effort for all those involved. Our eHealth interventions were successful in making patients' medication management support more efficiently. We supported patients with an electronic injection device that helped patients inject at home keeping some patients from burdening caregivers or having to go to the hospital (**Chapter 2**). Tele-monitoring gout flares using a smartphone app helped patients control disease activity: of the twenty flares that occurred in seventeen patients during the three-month study period, four led to a pro-active phone call and eventually one patient receiving additional ad-hoc care (**Chapter 3**). Although our serious game did not support patients with rheumatoid arthritis in becoming more adherent to medication, it could support patients in another way namely through engaging them with a serious game (**Chapter 6**). As advocated in this paragraph, there are two possible ways to take the serious game forward: aim to establish effectiveness or increase healthcare efficiency. Effectiveness could be increased by adjusting behaviour change techniques of the serious game intervention to improve clinical outcomes. Healthcare efficiency could be increased by valuing the serious game as a channel to communicate with patients and as such readjusting the intervention's aim. Either way, intervention effectiveness

on supporting medication management should be re-evaluated when intervention or aim changes, as would apply to other eHealth interventions.

Can all patients benefit from eHealth?

In this thesis inflammatory rheumatic diseases served as model for long-term conditions and therefore we would like to discuss generalisability of the results of studied test cases on three levels: i. patients with rheumatic diseases that did not participate in our studies, ii. patients with other long-term conditions and iii. specific patient populations (e.g. people with limited health literacy).

i. The findings of our studies do not necessarily apply to other patients with rheumatic diseases as our studies suffered from selection bias. Study participation was voluntary and therefore our study population consisted of patients that were receptive to eHealth (early adopters) and willing to perform research-related activities. In the overall population with rheumatoid arthritis, 38% of patients refuse to use eHealth while 29% to 66% already make use of eHealth for their rheumatoid arthritis.[9,14] In our study populations eHealth use was high: 57% (32/57) of patients preferred the electronic injection device over their previous device (**Chapter 2**), gout app adherence was 96% (2600/2710 queries) (**Chapter 3**) and 79% (87/110) of the intervention participants installed the serious game (**Chapter 6**). As the majority of patients with rheumatoid arthritis is receptive to eHealth and the uptake of our eHealth interventions was high, we belief eHealth is a suitable option for providing medication management support to a substantial number of patients. This belief is further strengthened by the fact that general characteristics of our study population such as age, sex and disease duration did not deviate from the overall population with a rheumatic disease.

ii. In this thesis we studied three aspects of medication support: medication use, monitoring disease and medication adherence. We will discuss generalisability to patients with other long-term conditions for each of these three aspects. In support of patients during medication use we studied an electronic injection device for injecting drug therapy at home across various rheumatological conditions (**Chapter 2**). As many people with rheumatic disease have low hand dexterity, the electronic injection device was developed to be used regardless of hand dexterity. Therefore the device can be applied in other conditions requiring drug injection such as diabetes provided the device can be suited to fit other drugs.

Our gout app tele-monitored disease activity of gout (**Chapter 3**). Tele-monitoring can benefit patients with chronic conditions that, like gout, follow an erratic course that can be influenced by patient and/or healthcare provider actions. Tele-monitoring has for example shown to be effective in controlling hypertension, diabetes type II and chronic obstructive pulmonary disorder.[12,15,16] For Parkinson's disease, a prime example of a condition with an erratic course, initial findings are encouraging but large-scale randomised controlled trials on clinically relevant outcomes are lacking.[17] Tele-monitoring has potential but effectiveness of tele-monitoring needs to be determined disease-specifically as each long-term condition has its own specific characteristics, clinical outcomes and patient populations. In addition, healthcare providers should be aware tele-monitoring shifts part of the care responsibility to patients. Patients need to be willing and capable to take on this responsibility in order of tele-monitoring to be viable support in patients' medication management.

Our systematic review already showed eHealth interventions can positively influence medication adherence across long-term conditions (**Chapter 4**). Despite the promising results of the systematic review, our serious game that targeted implicit attitudes in patients with rheumatoid arthritis failed to show a positive effect on medication adherence (**Chapter 6**). Implicit attitudes were targeted because Linn et al. previously showed these were negative and deviated from explicit attitudes in patients with rheumatoid arthritis.18 In order for the serious game to benefit other patients, the behavioural design thinking approach as recently published by Voorheis et al. (2022) should be re-evaluated.[19] In concrete terms, for behavioural design it should first be investigated what the implicit attitudes towards medication in the patient population are and during the design thinking process the users' needs and desires should be analysed. Even still, it should not be expected that serious games will be a solution for all patients as will be detailed in the next section.

iii. There is no one-size-fits-all channel for providing patient support and where eHealth might suit some patients it is a bad fit for others. Not everybody likes playing puzzles for example and this might be one of the reasons why the GAMER study had an inclusion rate of only 11% where similar studies reach 20% to 30% inclusion rate (**Chapter 6**). To appeal to other patients too, different game formats might be desirable. For example, serious games that stimulate balanced physical activity might be of interest to patients with rheumatoid arthritis[20] and a racing game might appeal more to children. Furthermore, patients with limited health literacy generally are at risk of having limited digital health literacy.[21] Nevertheless, eHealth can also provide opportunities for people with limited health literacy. For patients that have trouble remembering, exact instructions can benefit from on-screen instructions provided each injection by the electronic injection device (**Chapter 2**). For patients who prefer visual information delivery, the smartphone is a perfect channel as smartphones are omnipresent.[22,23] When developing an eHealth intervention there are two options: specifically target part of the population or designing the intervention for a broad a population as possible. Either way, this can be best achieved by actively involving patients during eHealth intervention development which we will attend to in the next section.

How can eHealth interventions in support of patients be sustained?

This question serves to translate the findings of this thesis to clinical practice and future research. Patients can only benefit from effective eHealth interventions if eHealth interventions are readily applied in healthcare. To achieve the application of eHealth interventions patients, healthcare providers and policy makers should adopt eHealth as possible solution to problems of individual patients and healthcare in general.[24] Apart from adoption by these parties: implementation, quality and costs are important aspects for integration and sustainability of eHealth interventions in healthcare.

In order to sustain eHealth interventions aimed at patients, they should be adopted by patients and – as discussed previously – these interventions should be tailored to patients' needs. Our eHealth interventions were well adopted by patients willing to take part in research: 57% (32/57) of patients preferred the electronic injection device (**Chapter 2**), gout app adherence was 96% (2600/2710 queries) (**Chapter 3**) and 79% (87/110) of the intervention participants installed the serious game (**Chapter 6**). Furthermore, the Technology Acceptance Model, a widely used model for studying patient acceptance in (digital) healthcare, was applied to assess patient acceptability.[25–27] According to the Technology Acceptance Model, actual intervention use is – in part – influenced by perceived ease of use and perceived usefulness.[25] Our eHealth interventions showed good ease of use. A possible explanation for the high adoption and good ease of use of our eHealth interventions is the thorough patient involvement. Patient involvement was stimulated and guided by patient participation panel STAP, a local initiative to stimulate patient involvement in research.[28] Patients were extensively involved in designing the interventions (**Chapter 2 & 5**) and partly involved in evaluating effectiveness of the interventions (**Chapter 3 & 6**). Apart from design and evaluation, patient involvement could have been more extensive by also involving patients during conception of eHealth interventions.[24,29] Possibly this could have led to better perceived usefulness of our interventions by patients as usefulness of the gout app was rated neutral to good (**Chapter 3**) and behaviour change tasks of the serious puzzle game were not considered useful for improving medication adherence (**Chapter 6**).

Next to patients, healthcare providers also play an important role in adoption of eHealth for medication management support. Patients are more likely to use eHealth interventions if healthcare providers offer eHealth interventions as possible support and dedicate part of their time in upholding/maintaining these interventions. Since eHealth is a time and location independent medium, healthcare delivery through eHealth can transcend consultation hours at the healthcare centre. Healthcare providers need to optimise their work processes in order to effectively implement eHealth. This is not an easy task, especially when in addition to running consultation hours, as we saw during the gout app feasibility trial (**Chapter 3**) where manning the clinician's dashboard – where flares of patients were monitored real-time – was troublesome at times. In other words: to sustain eHealth application in the long run and make it a (more) effective strategy, healthcare providers need to be eHealth-minded.[8,30]

Patient and healthcare provider adoption will ensure application of eHealth in clinical practice but to truly sustain eHealth, it should be adopted by policy makers too. Apart from providing a push towards clinical practice, eHealth adoption in policy ensures reimbursement for (the delivery of) eHealth and anchorage in the healthcare system. Even though the increasing gap between healthcare demand and healthcare provision is well-known to policy makers,[6] reimbursement for eHealth is only slowly advancing in the Netherlands. The urgency of the COVID-19 pandemic was needed to extend reimbursement policy for eHealth.[31] We could learn from policy makers in Germany who pushed eHealth to clinical practice by introducing eHealth on prescription: healthcare providers can prescribe patients eHealth interventions as remedy for their health issues. Although prescribing eHealth is not widely adopted by healthcare providers yet,[32] German policy makers have enabled access to eHealth for healthcare providers and patients and as such added eHealth to the healthcare provision arsenal. Similarly, anchorage of eHealth in healthcare systems is progressing: the Dutch Ministry of Health, Welfare and Sport stated in 2022 that digital solutions should be the first solutions considered when providing support for elderly.[33] Simultaneously, the Dutch Public Health Council warns current innovation culture in Dutch healthcare is suboptimal and advises to restructure strategies, responsibilities and reimbursement policies.[34] The research in this thesis adds to lessons learnt on applying eHealth in support of patients. Adoption of eHealth by patients, healthcare providers and policy makers is a process that takes time: time to experiment with applying eHealth and exploring how to implement eHealth in daily practice.

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Implementation should be part of intervention effectiveness as a highly effective intervention that is hard/laborious to execute loses (part of its) effectiveness in daily practice. Evidence-based medicine makes healthcare providers reluctant to implement interventions that have yet to prove their value. As a result, both gout flare app (**Chapter 3**) and serious game (**Chapter 6**) were tested without integration in the rheumatological clinic. Because implementation and effectiveness are so closely related, it is advised to use a hybrid study design to simultaneously assess effectiveness and implementation factors as this could speed the translation of research findings into routine clinical practice.[35–37]

Quality of eHealth is another important aspect as the more reliant healthcare is on technology, the more reliable this technology should be. A striking example is the electronic injection device (**Chapter 2**) where device malfunctioning meant patients could not inject at the designated time. Unfortunately, technical issues were not an outcome parameter in this study and thus not described. During the trial some cartridges managed to get stuck in the device; for some patients this was reason to abandon using the electronic injection device after the trial. The other two studied eHealth interventions (**Chapter 3, 5 & 6**) were mobile applications which only suffered minor technical issues during the trial. As these interventions only consist of software, it is easier to pre-test intervention quality and resolve issues even after the design phase. While the studies in this thesis were performed much has improved in quality assurance. In July 2021 ISO certification 82304-2 was published labelling eHealth quality on four domains: healthy and safe, easy to use, secure data and robust build.[38] Although certifying an app is not an easy task and requires effort from both designers as certifying bodies, our findings stress its importance. What is more, clear labelling of mobile application quality allows patients to better judge the advantages and disadvantages of eHealth interventions.

Sustaining eHealth also means bearing costs that come with maintenance of eHealth interventions and the ICT infrastructure needed to keep eHealth accessible. Even though costs should not be underestimated, scalability of eHealth means it can outperform human resources in time, effort and money. Therefore cost-effectiveness could also be one of the possible benefits of eHealth and an outcome to consider during scientific research. It should be kept in mind costs precede benefits and thus applying eHealth in healthcare requires investments in both intervention development and implementation. In addition, benefits might not befall those who carry the costs. Both statements are illustrated by tele-monitoring gout flares (**Chapter 3**). Tele-monitoring might lead to more short-term healthcare provision and thus more costs as healthcare providers act upon flaring compared to consultations twice a year. Benefits are achieved when proactive care leads to less (disease) escalation and, in the case of gout, protects against comorbid cardiovascular disease which does not befall the rheumatology clinic.[39,40]

All in all, it is fair to say eHealth can be part of the solution if wielded properly. From what we have learned during performance of the studies in this thesis the following preconditions should be met to increase chances of proper wielding:

1. Apply eHealth as a means, not as a goal.
2. Involve patients in every step of healthcare innovation to ensure eHealth meets their needs.
3. There should always be alternatives to eHealth as eHealth is not for everyone.
4. Implementation is key and hybrid designs assessing eHealth interventions as well as factors for implementation are desired.

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Chapter 8

English summary

This thesis explored how eHealth can be applied to support patients with long-term conditions in managing their medication. Although medication is usually effective in treating health problems, it can also lead to drug-related problems. Drug-related problems are all events involving medication that actually or potentially lead to lack of effect or adverse drug events. Patients have a need for support in medication management to prevent drug-related problems as this can lead to an increase in quality of life and a decrease in healthcare burden. Due to the ageing population that uses more and more medication the demand on the healthcare workforce is increasing. It is predicted that the growth of the healthcare workforce is unable to meet this demand. In order to keep supporting patients in managing their medication, more efficient ways of healthcare provision are needed. eHealth - the use of information and communication technology in healthcare - could be such an efficient way as it allows time and location independent healthcare provision. Just like medication, eHealth only works when applied and implemented properly. Even though eHealth can be advantageous and its use is on the rise, scientific evidence about usability and effectiveness is lacking. Therefore, this thesis aimed to investigate how eHealth is experienced by patients and whether eHealth benefits medication management by patients.

This thesis looked at three eHealth interventions that support patients in various ways:
In **Chapter 2** an electronic self-injection device that could support patients in correctly administering medication was studied on patient preference and satisfaction. **Chapter 3** investigated the feasibility of tele-monitoring gout flares using a smartphone application. The rest of the thesis looked at effectiveness of eHealth on medication adherence. A systematic review on eHealth interventions for improving medication adherence was performed in **Chapter 4**. The development of a serious game intervention for improving medication adherence is described in **Chapter 5** and the effectiveness of this intervention is tested in a randomised clinical trial in **Chapter 6**. **Chapter 7** put the findings of this thesis in perspective and provided recommendations for clinical practice.

Chapter 2: Patient preference and satisfaction of an electronic injection device

Electronic self-injection device (e-Device) ava® has been developed in addition to the syringe or auto-click pen for anti-rheumatic drug certolizumab and aims to overcome some barriers to self-injection. The e-Device hides injection needle, can toggle injection speed and provides instructions at each injection. In **Chapter 2** patient satisfaction and preference of the e-Device were evaluated.

Patients were recruited from the Netherlands, Denmark and Sweden and trained to use the e-Device. Patients administered three consecutive self-injections using the e-Device after which their experience was assessed using the post-injection assessment of self-injection questionnaire. An additional questionnaire evaluated training materials and after the third injection patients indicated their preference: the e-Device or their previous device.

59 patients participated and most rated the e-Device highly for satisfaction, self-confidence and ease of use. The negative feelings and pain and skin reactions domains had low ratings. Patient experiences were similar following each of the three injections. Training materials were rated highly (video: 8.4/10; step-by-step guide: 8.4/10). 57% (32/56) of the patients preferred the e-Device over their previous self-injection device.

Patients were satisfied with the e-Device and most preferred it over other self-injection devices. By improving patient experiences, the e-Device can support patients in using medication at home.

Chapter 3: Feasibility of tele-monitoring gout flares using a smartphone app

Patients often experience flares at home, without the clinician knowing, which limits the timely and accurate monitoring of gout flares and, ultimately, limits adequate pharmacological treatment. Therefore, we developed a smartphone application (app) for patients to tele-monitor gout flares surveyed by clinicians and studied its feasibility in **Chapter 3**. The aim of this study was to assess patient acceptability and technical and clinical feasibility.

Adult patients with either established gout or high suspicion thereof were recruited if they possessed a smartphone and reported an arthritis attack in the past three months. A smartphone application was used to identify gout flares by asking during 90 consecutive days: (1) what is your pain score (0–10); (2) are your joints warm; (3) are your joints swollen; and (4) are you currently experiencing a gout flare? The clinician was alerted via email if a flare occurred. Patient acceptability was assessed using the Technology Acceptance Model. Technical feasibility consisted of reported technical issues and clinical feasibility of actions taken by the clinician regarding gout flare alerts.

Twenty-nine patients with a mean age of 57 years and all but one male completed the study. Adherence rate to the daily questions was 96% (2800/2910). Patients had a positive attitude towards app use, found the app very easy to use (mean usability score 81 out of 100) and were neutral to positive on its usefulness. There were four minor technical issues. A total of 100 gout flare alerts were generated that led to 18 proactive contacts with patients.

A smartphone app to monitor gout flares was developed and tested, showing high adherence, good acceptability and clinical feasibility for established gout patients. The app has potential to support patients with gout by home-monitoring their gout flares allowing the care team to aid patients when needed.

Chapter 4: A systematic review on effect of eHealth interventions on medication adherence

Medication nonadherence leads to suboptimal treatment outcomes, making it a major priority in healthcare. eHealth provides an opportunity to offer medication adherence interventions with minimal effort from healthcare providers whose time and resources are limited. Therefore, we performed a systematic review in **Chapter 4** that aimed to: (1) evaluate effectiveness of recently developed and tested interactive eHealth interventions on medication adherence in adult patients using long-term medication and (2) describe strategies among effective interventions.

Five scientific databases were systematically searched from January 2014 to July 2019 as well as reference lists and citations of included articles. Eligible studies fulfilled the following inclusion criteria: (1) randomized controlled trial with a usual care control group; (2) a total sample size of at least 50 adult patients using long-term medication; (3) applying an interactive eHealth intervention aimed at the patient or patient's caregiver; and (4) medication adherence as primary outcome. Methodologic quality was assessed and a best evidence synthesis performed because studies were too heterogenous to perform a meta-analysis.

Twenty-two randomized clinical trials were included reporting on twenty-nine interventions. A majority of these (17/29) interactive interventions improved medication adherence with a statistically significant effect ($P<.05$). Our best evidence synthesis provided strong evidence for a positive effect of interventions using SMS text messages or interactive voice response, mobile app, and calls as mode of providing adherence tele-feedback. Intervention strategies "to teach medication management skills," "to improve healthcare quality by coordinating medication adherence care between professionals," and "to facilitate communication or decision-making between patients and healthcare providers" also showed strong evidence for a positive effect.

Overall, this review supports the hypothesis that interactive eHealth interventions can be effective in improving medication adherence. Intervention strategies that improve patients' treatment involvement and their medication management skills are most promising and should be considered for implementation in practice.

Chapter 5: Development of a serious puzzle game aimed at improving medication adherence

Patients' implicit attitudes toward medication need and concerns may influence their adherence. Targeting these implicit attitudes by combining game-entertainment with medication-related triggers might improve medication adherence in patients with rheumatoid arthritis (RA). In **Chapter 5** the systematic development of a serious game to enhance adherence to disease-modifying anti-rheumatic drugs (DMARDs) by using intervention mapping is described.

The intervention mapping process was guided by a multidisciplinary expert group and proceeded along 6 steps: (1) exploring the problem by assessing the relationship between medication adherence and implicit attitudes, (2) defining change objectives, (3) selecting evidence-based behaviour change techniques that focused on adjusting implicit attitudes, (4) designing the intervention, (5) guaranteeing implementation by focusing on intrinsic motivation, and (6) planning a scientific evaluation.

Based on the problem assessment and guided by the Dual-Attitude Model, implicit negative and illness-related attitudes of patients with RA were defined as the main target for the intervention. Consequently, the change objective was "after the intervention, participants have a more positive attitude toward antirheumatic drugs." Attention bias modification, evaluative conditioning, and goal priming were the techniques chosen to implicitly target medication needs. These techniques were redesigned into medication-related triggers and built in the serious puzzle game. Thirty-seven patients with RA tested the game at several stages. Intrinsic motivation was led by the self-determination theory and addressed the 3 needs, that is, competence, autonomy, and relatedness. The scientific evaluation is described in **Chapter 6**.

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Chapter 6: Gaming for Adherence to Medication using Ehealth in Rheumatoid arthritis (GAMER) study

A multicentre randomised controlled trial (RCT) was performed with adults with RA that used DMARDs and possessed a smartphone/tablet to assess the effect of playing the serious game on improving DMARD medication adherence. Control and intervention groups received care as usual. The intervention group played the serious game at will during three months. Game play data and online questionnaires on medication (CQR, BMQ) and clinical outcomes (HAQ and RADAI) were collected. Primary outcome was DMARD implementation adherence operationalised as the difference in proportion of non-adherent participants (<80% taking adherence) between intervention and control group after three months.

Of the 110 intervention participants that started the study, 87 participants (79%) installed the game and had a median playtime of 9.7 hours at three months. Overall, 186 participants completed the study. Adherence in intervention group (63%) and control group (54%) did not differ significantly (p = 0.26) at three months. Neither did CQR continuous score (p = 0.20), beliefs about medication (p = 0.43) nor clinical outcomes (HAQ: p = 0.97; RADAI: p = 0.90).

A serious game aimed at reinterpreting attitudes toward medication failed to show an effect on adherence to DMARDs or clinical outcomes in patients with RA. The game was played frequently indicating that it can be an effective channel for reaching patients.

Chapter 7: General discussion

The findings of this thesis were put in perspective by debating three questions:

- How can eHealth help solve problems related to patients' medication management?
  eHealth can facilitate dissolving problems related to patients' medication management through reducing drug-related problems and/or providing medication management more efficiently. In order to achieve this the aim of eHealth should be clear and the intervention tailored to patients' needs.
- Can all patients benefit from eHealth?
  The results of our research are also applicable to other patients outside those we studied being with rheumatic diseases or other long-term conditions. Nevertheless, eHealth is not a one-size-fits-all channel and part of the population cannot be reached by eHealth. To increase eHealth's outreach, eHealth should either be designed to fit as many people as possible or specifically target part of the population.
- How can eHealth interventions in support of patients be sustained?
  eHealth interventions can be sustained if they are adopted by patients, healthcare providers and policy makers alike and care has been taken to guarantee implementation, quality and cost control.

In conclusion

How do patients experience eHealth interventions?

Overall, patients found the tested eHealth interventions easy to use. Perceptions on the usefulness of the eHealth interventions varied considerably. As a result, part of the patient population accepts applying eHealth interventions in support of their long-term medication use (**Chapter 2, 3, 5 & 6**).

Do eHealth interventions benefit medication management by patients?

eHealth interventions do benefit medication management by patients in part as:

- Over half of the patients prefer using an electronic injection device for injecting the biological certoluzimab pegol compared to syringe or auto-click pen (**Chapter 2**).
- Tele-monitoring gout flares by patients is feasible and supports established gout patients in managing their disease and associated medication (**Chapter 3**).
- eHealth interventions can effectively influence long-term medication adherence through improving patients' treatment involvement and their medication management skills (**Chapter 4**). However, a serious puzzle game that we developed targeting patients' implicit attitudes of medication taking behaviour was not effective in improving medication adherence or clinical outcomes in patients with established rheumatoid arthritis (**Chapter 5 & 6**).

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Chapter 9

Dutch summary (lekensamenvatting)

Hoofdstuk 1: Introductie

Veel chronische aandoeningen worden behandeld met medicijnen. Medicijnen zorgen voor een betere kwaliteit van leven onder andere door vermindering van klachten. Naast deze voordelen kunnen medicijnen ook nadelen hebben: het kan bijvoorbeeld lastig zijn om ze goed te gebruiken of er kunnen bijwerkingen optreden. Deze nadelen worden geneesmiddelgerelateerde problemen genoemd. Mensen worden steeds ouder en gebruiken daarom steeds meer medicijnen. Hierdoor neemt de kans op geneesmiddelgerelateerde problemen toe. Daarnaast groeit het aantal zorgmedewerkers niet mee met deze toenemende vraag van zorg. Door de toename in geneesmiddelgerelateerde problemen en de verminderde beschikbaarheid van zorgpersoneel wordt het in de toekomst steeds lastiger geneesmiddelgerelateerde problemen te voorkomen of aan te pakken. Daarom moeten we slimme en efficiënte oplossingen bedenken om geneesmiddelgerelateerde problemen blijvend aan te kunnen pakken.

Eén van die mogelijke manieren om patiënten te ondersteunen is door het gebruik maken van eHealth. eHealth is de toepassing van Informatie en Communicatie Technologie (ICT) in de zorg. Denk hierbij aan medicijnwekker-apps op de telefoon of bloeddrukmeters die de bloeddruk van thuis naar het ziekenhuis sturen. Andere voorbeelden van eHealth zijn beeldbellen of een sensor op de huid die continu de bloedsuiker meet. eHealth kan efficiënt zijn omdat het op elke plaats en elk tijdstip te gebruiken is. Dat betekent dat patiënten het thuis kunnen gebruiken terwijl de zorgverlener in haar zorgcentrum is en dus kan eHealth (reis)tijd schelen. Bovendien kunnen patiënten eHealth gebruiken wanneer het hen uitkomt en zijn ze niet afhankelijk van de momenten dat er een afspraak is met de zorgverlener.

Ondanks deze voordelen heeft eHealth, net als medicijnen, ook nadelen als het niet goed wordt toegepast. eHealth toepassingen moeten technisch goed werken en het doel bereiken waar ze voor ontwikkeld zijn. Daarnaast moeten patiënten de eHealth toepassing ook (willen en kunnen) gebruiken. Om zeker te weten dat eHealth toepassingen voldoen aan deze drie eisen is het belangrijk om hier onderzoek naar te doen.

Tabel 1. Globale omschrijving van de eHealth toepassingen die onderzocht zijn in dit proefschrift

eHealth toepassing	Ondersteunt bij	Onderzocht in	Beschreven in	Waar het onderzoek naar gekeken heeft
Elektronische injectiepen	Medicijn gebruik	59 patiënten met reumatische aandoeningen	Hoofdstuk 2	Patiënttevredenheid Patiëntvoorkeur
App die dagelijks naar jicht klachten vraagt	Volgen van de ziekteactiviteit	29 patiënten met jicht	Hoofdstuk 3	Patiëntacceptatie Technische stabiliteit Toepasbaarheid in de zorg
Puzzelapp 'Medi en Seintje'	Therapietrouw	229 patiënten met reumatoïde artritis	Hoofdstuk 5 Hoofdstuk 6	Patiëntacceptatie Werkzaamheid

In dit proefschrift hebben we onderzoek gedaan naar drie verschillende eHealth toepassingen in de reumazorg die patiënten op verschillende manieren ondersteunen bij hun medicijngebruik (zie tabel 1). Dit onderzoek geeft antwoord op twee centrale vragen:
1) Hoe ervaren patiënten deze eHealth toepassingen?
2) Zijn de eHealth toepassingen van meerwaarde voor de patiëntenzorg?

In hoofdstuk 2 hebben we gekeken hoe tevreden patiënten zijn met het gebruik van een elektronische injectiepen voor het injecteren van hun reumamedicijn en welk vorm van injecteren de voorkeur heeft. Hoofdstuk 3 beschrijft een pilotonderzoek bij patiënten met jicht of een verdenking op jicht. Hier onderzochten we wat patiënten vinden van het dagelijks bijhouden van hun klachten, of de app technisch werkt en of het toepasbaar is in de zorg voor patiënten met jicht. De rest van het proefschrift gaat in op het verbeteren van therapietrouw door het toepassen van eHealth. Daarvoor hebben we een overzichtsartikel opgeschreven in hoofdstuk 4 waarin alle eHealth toepassingen voor het verbeteren van therapietrouw bij elkaar zijn gezet. Vervolgens beschrijven we in hoofdstuk 5 de ontwikkeling van puzzelapp 'Medi en Seintje' die naast puzzelen ook inzet op het verbeteren van therapietrouw van reumamedicijnen. In hoofdstuk 6 hebben we getest of puzzelapp 'Medi en Seintje' de therapietrouw van patiënten met reumatoïde artritis verbetert. In hoofdstuk 7 bediscussiëren we de resultaten van al het onderzoek en bespreken we of de resultaten ook gelden voor andere chronische aandoeningen dan reuma. We sluiten af met de eindconclusies van dit proefschrift.

Hoofdstuk 2: Patiënttevredenheid en voorkeur voor elektronische injectiepen ava®

De elektronische injectiepen ava® is ontwikkeld als aanvulling op de twee andere type injectiepennen die gebruikt worden om een reumamedicijn te injecteren. Patiënten kunnen voordeel hebben van ava® omdat de injectiesnelheid elektronisch ingesteld kan worden, de naald niet zichtbaar is en het injecteren geen kracht kost. We hebben patiënten in Nederland, Denemarken en Zweden gevraagd om ava® minimaal drie keer te gebruiken. Na elke injectie vulden de patiënten een vragenlijst in. Na de derde injectie werd ook gevraagd of ava® de voorkeur had boven andere injectiepennen. In totaal hebben 59 patiënten deelgenomen aan het onderzoek. Patiënten vonden ava® makkelijk te gebruiken en waren er tevreden en zelfverzekerd over. Daarnaast deed het injecteren weinig pijn en waren er geen/weinig huidreacties na injectie. Er was geen verschil in scores tussen de drie injecties. Tweeëndertig van de 56 patiënten (57%) gaven de voorkeur aan ava® boven andere injectiepennen. Dat betekent dat ava® een deel van de patiënten kan ondersteunen bij het gebruik van medicatie thuis.

Hoofdstuk 3: Jichtaanvallen bijhouden met de smartphone – een eerste proef

Jichtaanvallen zijn erg pijnlijk en belemmerend in het dagelijks leven. Ze ontstaan meestal als patiënten thuis zijn en niet als ze in de spreekkamer bij de arts zitten. Patiënten weten vaak weken later niet meer hoe vaak ze een aanval gehad hebben en hoe die verlopen is. Patiënt en reumatoloog hebben daarom niet altijd een goed beeld over het verloop van de jicht en dat het maakt het moeilijk om jicht goed te behandelen. Daarom hebben we een smartphone app ontwikkeld waarbij patiënten met jicht of een verdenking op jicht gedurende drie maanden elke dag vragen beantwoorden. De eerste vraag was: 'wat is je pijnscore van 0 tot 10?'. Bij een score van vier of hoger kregen patiënten drie vervolgvragen: 'zijn je gewrichten warm?', 'zijn je gewrichten gezwollen?' en 'denk je dat je op dit moment een jichtaanval hebt?'. Het onderzoeksteam kon de antwoorden meteen inzien via een dashboard en kreeg bericht op het moment dat er waarschijnlijk sprake was van een jichtaanval. Negenentwintig patiënten hebben de app getest en hebben 96% van de vragen beantwoord. Patiënten vonden de app makkelijk in gebruik en waren neutraal tot positief over het nut ervan. Patiënten vonden het fijn dat de arts direct kon inzien of er sprake was van pijn. Er waren vier kleine technische problemen tijdens het onderzoek die makkelijk opgelost konden worden. In totaal hebben 100 mogelijke jichtaanvallen geleid tot 18 contacten met patiënten. Bij patiënten met een verdenking op jicht werden veel mogelijke jichtaanvallen door de app gemeld zonder dat dit tot contact met patiënten leidde. De app is daarom minder geschikt voor patiënten met een verdenking op jicht. De app lijkt vooral van toegevoegde waarde voor patiënten met jicht die een aanhoudende jichtaanval hebben omdat er dan proactief actie ondernomen kan worden vanuit het ziekenhuis.

Hoofdstuk 4: Een overzicht van alle recente onderzoeken naar eHealth toepassingen voor het verbeteren van therapietrouw

Therapietrouw is de mate waarin het een patiënt lukt om medicatie te gebruiken zoals overeengekomen met de zorgverlener. Therapietrouw is een belangrijk thema in de gezondheidszorg; een medicijn dat niet (goed) wordt ingenomen zal immers niet goed werken. Omdat we wilden weten of eHealth kan bijdragen aan het verbeteren van de therapietrouw, hebben we alle recente onderzoeken die gedaan zijn naast elkaar gezet. Uit de hiervoor gangbare databronnen kwamen 9.047 mogelijk geschikte wetenschappelijke artikelen naar voren. Na grondige selectie bleven er 21 artikelen over. In deze 21 artikelen werden de effecten van 29 eHealth toepassingen beschreven en vergeleken met de effecten van de gebruikelijke behandeling. Uit het overzicht blijkt dat eHealth ingezet kan worden om patiënten met een chronische aandoening te ondersteunen bij het trouw innemen van hun medicijnen. Het sterkste bewijs hiervoor vonden we bij eHealth toepassingen via SMS-berichten, mobiele apps en telefoongesprekken. Bij de eHealth toepassingen zijn verschillende strategieën gebruikt. Niet alle strategieën zijn even geschikt voor het verbeteren van therapietrouw. Strategieën die wel werken, zijn de volgende:

- patiënten vaardigheden aanleren: bijvoorbeeld met een app waar inname van bloeddrukverlagers en de bloeddruk worden bijgehouden zodat patiënten het effect van de medicijnen leren zien;
- patiënten helpen met keuzes maken rondom medicatie: bijvoorbeeld door het voeren van een telefoongesprek met de apotheker over barrières bij het innemen van medicatie en vervolgens advies over hoe die barrières weggenomen kunnen worden;
- verbeteren van kwaliteit van zorg: bijvoorbeeld doordat huisarts en apotheker gezamenlijk op de hoogte worden gebracht van het missen van meerdere innames door een 'slimme' medicijnverpakking die berichten naar deze zorgverleners stuurt.

Hoofdstuk 5: De ontwikkeling van puzzelapp 'Medi en Seintje'

Er zijn vele redenen waarom patiënten minder trouw hun medicijnen nemen dan overeengekomen met de zorgverlener. Veel (eHealth) toepassingen focussen op dezelfde 'bewuste' factoren: herinneren van inname, bijspijkeren van kennis of het stimuleren van samen beslissen tussen patiënt en zorgverlener. Uit eerder onderzoek is echter gebleken dat ook onbewuste factoren een rol kunnen spelen. Dit zijn afwegingen die gemaakt worden zonder dat we hier bewust over nadenken en worden impliciete attitudes genoemd. Het blijkt dat het merendeel van de patiënten met reumatoïde artritis bewust positief is over medicatie (bijvoorbeeld door te uiten dat medicatie hen helpt) maar onbewust negatief is over medicatie. Dit laatste blijkt uit testen die de houding ten overstaan van reuma medicatie meten op zo'n hoge snelheid dat er geen tijd is voor bewust nadenken. Wij wilden daarom een eHealth toepassing ontwikkelen die juist positieve onbewuste afwegingen kan maken of versterken. In een multidisciplinair team hebben we een puzzelapp ontwikkeld met daarin vier puzzeltypes (kruiswoord, woordzoeker, sudoku en tangram) in drie moeilijkheidsgraden.

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De poppetjes Medi (een tablet) en Seintje (een capsule) kleurden de spelomgeving en gaven de puzzelinstructies. Om de positieve onbewuste afwegingen te versterken, werden er taken toegevoegd aan de spelomgeving. Deze taken moest een speler doen om het spel te openen of een nieuwe puzzel te laden (na minstens 10 minuten spelen). Deze taken waren gebaseerd op gedrag veranderende technieken. Een voorbeeld: de speler werd gevraagd om een pil bovenin het scherm naar een plaatje van een mond te slepen onderin het scherm. Het is namelijk aangetoond dat de aantrekkingskracht van een voorwerp versterkt wordt op het moment dat iemand dit herhaaldelijk naar zich toetrekt. Het spel is op verschillende momenten door in totaal 37 patiënten met reumatoïde artritis getest om te garanderen dat het spel ook aansluit bij de doelgroep.

Hoofdstuk 6: Het effect van puzzelapp 'Medi en Seintje' op therapietrouw aan reumamedicijnen

Na het ontwikkelen van puzzelapp 'Medi en Seintje', hebben patiënten uit zes ziekenhuizen in Nederland getest of het spelen van de puzzelapp leidt tot een betere inname van reumamedicijnen. In totaal zijn 229 patiënten met reumatoïde artritis door loting verdeeld over een puzzelgroep (113 deelnemers) en een controlegroep (116 deelnemers). Gedurende drie maanden ontving de puzzel groep gebruikelijke zorg plus de puzzelapp, de controlegroep alleen gebruikelijke zorg. De puzzelgroep werd gevraagd om de app te installeren en naar eigen wens te spelen. Patiënten vulden na één en na drie maanden vragenlijsten in over therapietrouw en ziektebeleving. Ook werd de speeltijd bijgehouden. Honderdzesentachtig patiënten voltooiden de studie. Van de 85 puzzelgroep deelnemers die de studie afrondden, speelden 70 deelnemers (82%) minimaal één uur en 42 deelnemers (50%) langer dan 9,5 uur. Driekwart van de deelnemers waren na 40 dagen nog actief op de puzzelapp. De puzzelgroep was na drie maanden niet méér therapietrouw dan de controlegroep en er was ook geen verschil in ziektebeleving. Hoe vaak een patiënt het puzzelspel speelde maakte daarbij niet uit. Het spelen van 'Medi en Seintje' had dus geen effect op de reumatoïde artritis. Het spel werd door een deel van de patiënten wel veel gespeeld en kan dus een geschikt kanaal zijn om patiënten te bereiken.

Hoofdstuk 7: Discussie rondom onze bevindingen

In de discussie plaatsen we de resultaten uit dit proefschrift in een breder perspectief. Dit doen we door drie vragen te beantwoorden.

Hoe kan eHealth de problemen rondom medicatiegebruik door patiënten het beste oplossen?
Er zijn meerdere mogelijkheden voor eHealth om de problemen rondom medicatiegebruik door patiënten op te lossen. Zo kan eHealth de huidige zorg verbeteren bijvoorbeeld door de patiënt te begeleiden bij het injecteren van medicatie of door het bijhouden van ziekteactiviteit of therapietrouw. Een andere mogelijkheid voor eHealth is om de zorg efficiënter te maken door bijvoorbeeld tijd of kosten te besparen door het gebruik van technologische oplossingen. Het mooiste is als eHealth de zorg verbetert EN efficiënter maakt.

Kunnen alle patiënten baat hebben bij het gebruik van eHealth?
Onze onderzoeken naar eHealth toepassingen in de reumatologie zijn voor een groot gedeelte te vertalen naar andere aandoeningen omdat daar dezelfde problemen spelen zoals moeite met injecteren of verminderde therapietrouw. Toch zullen nooit alle patiënten baat hebben bij het gebruik van eHealth omdat er altijd mensen zijn die niet met eHealth kunnen of willen omgaan. Door eHealth toepassingen heel gericht te ontwikkelen voor een deel van de populatie, bijvoorbeeld voor mensen met beperkte gezondheidsvaardigheden, blijft de groep mensen die geen baat heeft bij eHealth zo klein mogelijk.

Hoe kunnen eHealth toepassingen langdurig ingezet worden in de praktijk?
Allereerst moeten patiënten en zorgverleners gewend raken aan het gebruik van eHealth en het consequent zien als mogelijke oplossing voor een probleem. Hierdoor zal eHealth langzaam onderdeel worden van standaardzorg. Ook beleidsmakers moeten oog hebben voor eHealth. In Nederland gebeurt dat steeds meer, al moet er dan wel voor gezorgd worden dat eHealth toepassingen juist worden ingezet. Voor de juiste duurzame inzet van eHealth is implementatie van groot belang en dit moet daarom meer worden meegenomen in het onderzoek naar eHealth. Daarnaast moet eHealth van goede kwaliteit zijn, hier helpt de recente ISO-norm voor eHealth bij. Als laatste stippen we ook financiën aan: men moet er rekening mee houden dat de kosten van eHealth zoals nieuwe apps en het aanpassen van de zorg voor de baten (beter/efficiëntere zorg) uit gaan.

Eindconclusie

Samengevat kan gesteld worden dat eHealth een onderdeel van de oplossing voor geneesmiddelgerelateerde problemen kan zijn als het juist wordt toegepast voor de juiste doelgroep. Wat we geleerd hebben tijdens dit onderzoek is dat de volgende voorwaarden de kans op het juist toepassen van eHealth vergroten:

1. Gebruik eHealth als middel, niet als doel.
2. Betrek patiënten in elke stap van zorginnovatie zodat eHealth aansluit bij hun behoeften.
3. Zorg altijd voor alternatieven voor eHealth aangezien eHealth niet voor iedereen geschikt is.
4. Wees al tijdens de onderzoeksfase bezig met de implementatie van eHealth.

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Research data management

Research data management

General information about the data collection

This research followed the applicable laws and ethical guidelines. Research Data Management was conducted according to the FAIR principles. The paragraphs below specify in detail how this was achieved.

Ethics

Chapter 2, Chapter 3, Chapter 5 and Chapter 6 of this thesis are based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The study protocols of Chapter 2, Chapter 3, Chapter 5 and Chapter 6 were submitted to the Medical and Ethical Review board Committee (MREC) on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, The Netherlands. The MREC region Arnhem Nijmegen provided a waiver for ethical approval for the study protocols of Chapter 2, Chapter 5 and Chapter 6. The study protocol of Chapter 3 was approved by the ethics committee under registration number NL65917.091.18. All patients described in this thesis provided written informed consent prior to being included in the study.

The studies described in this thesis received various grants from pharmaceutical industry. Chapter 2 was funded by UCB Pharma. Chapter 3 was funded by AbbVie Inc. and The Menarini Group. Chapter 6 was funded by AbbVie Inc. In addition, the serious game was a joint-venture by Sint Maartenskliniek, Games Solutions Lab and AbbVie Inc. None of the pharmaceutical companies that provided grants had any influence on the conduct, results or interpretation of findings of these studies.

FAIR principles

Findable: Data were stored on the server of the research department at the Sint Maartenskliniek. The paper case report forms were stored at the research department and, when finishing this thesis, subsequently transferred to the department's archive. Data sets and documentation to describe the data sets can be found on the department's server at V:\research_reuma_studies.

Accessible: All data will be available on reasonable request by contacting the staff secretary of the research department at the Sint Maartenskliniek (secretariaat.research@maartenskliniek.nl) or the corresponding author.

Interoperable: Documentation was added to the data sets to make the data interpretable. The documentation contains links to publications, references to the location of data sets and description of the data sets. The data were stored in the following formats: .xlsx (Microsoft Office Excel), .dta and .do (STATA). Data from Chapter 2, 3, 4, 5 and 6 were converged to Microsoft Excel and STATA for analyses.

Reusable: The data will be saved for 15 years after termination of the study concerned. Using these patient data in future research is only possible after a renewed permission by the patients as recorded in their informed consents (if applicable).

Privacy

The privacy of the participants in this thesis has been warranted using encrypted and unique individual subject codes. The encryption key was stored separately from the research data and was only accessible to members of the project who needed access to it because of their role within the project.

List of publications

List of publications

Part of this thesis

Pouls, B. P. H., Kristensen, L. E., Petersson, M., van den Bemt, B. J. F., Ballerini, L., Bruggraber, R., Karlen, H., Mountian, I., van Bracht, E., Wiegratz, S., & Jørgensen, T. S. (2020). A pilot study examining patient preference and satisfaction for ava®, a reusable electronic injection device to administer certolizumab pegol. Expert opinion on drug delivery, 17(5), 705–711.

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- *Awarded the best oral communication prize at the 2021 PRISMA conference.*

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- *Awarded the best abstract prize at the 2022 EULAR conference.*

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Voshaar N. E-health bevordert therapietrouw. Reumamagazine 2021(1).

Wapenaar J. Hoe e-health je patiënt therapietrouw kan maken. Nursing 2021-03-02.

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Dallinga M. Podcast Verder in Beweging: medicatiezorg en e-health. Sint Maartenskliniek 2022-06-14.

Voshaar N. Spelen om medicijnen trouw in te nemen. ReumaMagazine 2022(6).

Scientific publications outside this thesis

Hazen, A., Sloeserwij, V., **Pouls, B.**, Leendertse, A., de Gier, H., Bouvy, M., de Wit, N., & Zwart, D. (2021). Clinical pharmacists in Dutch general practice: an integrated care model to provide optimal pharmaceutical care. International journal of clinical pharmacy, 43(5), 1155–1162. https://doi.org/10.1007/s11096-021-01304-4

van der Nat, D. J., Huiskes, V. J. B., Taks, M., **Pouls, B. P. H.**, van den Bemt, B. J. F., & van Onzenoort, H. A. W. (2022). Usability and perceived usefulness of patient-centered medication reconciliation using a personalized health record: a multicenter cross-sectional study. BMC health services research, 22(1), 776. https://doi.org/10.1186/s12913-022-07967-7

PhD portfolio

PhD portfolio

Department: Pharmacy
Graduate School: Radboud Institute for Health Sciences
PhD period: 01-05-2018 – 01-09-2022
Promotors: Prof. dr. B.J.F. van den Bemt, Prof. dr. A.M. van Dulmen
Copromotors: Dr. J. Vriezekolk, Dr C.L. Bekker

Training activities	Hours
Courses	
- RIHS - Introduction course for PhD candidates (2019)	15
- RU - Beginners' course 'Statistics with JASP' for PhD candidates (2019)	45
- Radboudumc - eBROK course (for Radboudumc researchers working with human subjects) (2019)	26
- Radboudumc - Scientific integrity (2019)	20
- Writing retreat (2020)	56
- RU - Analytic Storytelling (2020)	20
- RU - Effective Writing Strategies (2020)	75
- Regression Techniques (2020)	36
- Multi-level analysis (2021)	18
Seminars	
- Lecture on scientific integrity (2018)	2
- Lecture on treatment of rheumatoid arthritis (2019)	4
- Lecture on missing data (2019)	2
- FIP challenges: digital health (2021)	2
- FIP: Selfcare in the digital age (2021)	2
- Research Lunch (2022)	28
- Art of Writing (2022)	28
- Journal Club (2022)	28
Conferences	
- 47th European Symposium on Clinical Pharmacy (2018) – oral presentation & workshop	28
- European Congress of Rheumatology (2019)	28
- 48th European Symposium on Clinical Pharmacy (2019) – poster presentation & workshop	28
- ISPOR conference 2019 Copenhagen (2019) – poster presentation	14
- Nederlandse Ziekenhuisfarmacie Dagen (2019) – oral presentation	14
- ESPACOMP online conference (2020) – oral presentation	14
- PRISMA symposium 2021 (2021) – oral presentation	14
- ESPACOMP online conference (2021) – oral presentation	14
- PRISMA symposium 2022 (2022) – oral presentation	14
- European Congress of Rheumatology (2022) – oral presentation	28
Other	
- Special Interest Group council member of the European Society of Clinical Pharmacists (2020 – 2022)	96

Teaching activities	Hours
Lecturing	
- Seminar eHealth (2020)	4
- Workshop eHealth in pharmacy practice x3 (2021)	24
- Seminar eHealth x2 (2021)	12
- Hackathon pharmaceutical care innovation (2022)	8
- Workshop eHealth in pharmacy practice (2022)	8
- Seminar eHealth x3 (2022)	12
Supervision of internships / other	
- Supervision of a Bachelor student (2019)	56
- Supervision of a Master student (2020)	56
- Supervision of a Bachelor student (2022)	56
Total	**935**

Curriculum vitae

Curriculum vitae

Bart Pouls started his career in 2013 as medication reviewer in Service Apotheek Woerden and lecturer Pharmaceutical Technology and Manufacturing at Utrecht University after graduating from the Master of Pharmacy at that same university.

Early 2014 Bart entered the POINT programme that pioneered with installing a clinical pharmacist in general practice. He worked in the general practice in Maarn for 15 months when the programme ended. Half-way through 2015 Bart explored the pharmaceutical care services for the intellectually disabled as pharmacist at the long-term care facilities of the Amarant Groep in Tilburg.

At the start of 2017 Bart continued with lecturing various health disciplines on pharmacotherapy and communication. Additionally, he provided consulting services for MedApp, a mobile application that aimed to increase medication adherence through advancing medication alarms.

Bart went on to work for the Sint Maartenskliniek as part-time researcher and part-time pharmacist for institutions for elderly and intellectually disabled. In the course of 2018 Bart became a full-time PhD student investigating various eHealth applications within rheumatological care.

In 2019 Bart stood at the cradle of Vitae Maximus, a company that provides tailored health supplements in a multidose dispensing system. This is also when he became an active member of the European Society of Clinical Pharmacists and mentored several refugee students and professionals for the Universiteit Asiel Fonds (UAF) foundation.

When his PhD came to a close, Bart assisted the Dutch hospital pharmacist association (NVZA) with writing grant proposals and performing pilot studies for improving medication adherence of oral oncolytics. In 2022 he started as a lecturer Pharmacology and Toxicology at the Radboudumc.

A word of thanks

A word of thanks

There is only one way to say this
Humble. I stand, musing in bliss
A little help from my friends
Nurture fruits of the spirit, time escaping
Keen that it is only partly of my making

You delivered when I was demanding
Opened up opportunities, mind-expanding
Unscientifically unified in understanding

An industry of people science remarkably united
Like a jigsaw falling into place, image clear-sighted
Let it assume form, it feels so excited

Theses Sint Maartenskliniek

Theses Sint Maartenskliniek

Mulder, M. (2022). *Going off-road. Exploring and mapping psoriatic arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

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Tweehuysen, L. (2018). *Optimising biological treatment in inflammatory rheumatic diseases. Predicting, tapering and transitioning.* Radboud University Nijmegen, Nijmegen, The Netherlands.

Geerdink, Y. (2017). *Getting a grip on hand use in unilateral cerebral palsy.* Radboud University, Nijmegen, The Netherlands.

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