Anne M.M. Loohuis

App-based treatment for female urinary INCONTINENCE

Evidence based eHealth as an alternative to care-as-usual

STELLINGEN

1. Een app-behandeling voor ongewild urineverlies bij vrouwen is een werkzaam en kostenbesparend alternatief voor de bestaande standaard zorg. (Dit proefschrift)

2. Werving van patiënten via sociale media is erg geschikt voor onderzoek naar ziekten waar een taboe op heerst. (Dit proefschrift)

3. De extra functies die een app kan bieden zijn niet voor elke patiënt een toevoeging en kunnen zelfs belemmerend werken voor het uiteindelijk effect van de behandeling. (Dit proefschrift)

4. Het personaliseren van de keuze tussen app-behandeling en standaard zorg door middel van een predictiemodel verhoogt potentieel het effect van behandeling op zowel individueel niveau als op groepsniveau. (Dit proefschrift)

5. “An app is not a drug with one active ingredient, it is a complex intervention and should be developed and evaluated as such.” (Craig et al. 2008)

6. “Deciding how to do your research depends on a clear understanding of why you are doing the research.” (Morgan DL)

7. The solution to evidence based eHealth should not lie in study designs that are more practical and fast but of lower quality, it should rather lie in high-quality study designs assessing the principles underlying treatment effect with generalizability to other eHealth-interventions.

8. An app-based treatment needs continuous development and evaluation.

9. There is need for central regulation, support and guidance of evidence based eHealth, to guard quality of the interventions and to guide end-users to the available effective treatment options, including care-as-usual.

10. An app-based treatment for UI could also improve care-as-usual and lower taboo by creating awareness, normalizing the condition, and empowering women to demand sufficient treatment.

11. “The true outcome of research is determined by the influence it has had and the changes in society it has ignited.”(Holmberg) “Je wil in de telegraaf komen.”(te Winkel, persbureau UMCG)

12. “Twijfel is het begin van wijsheid.” (Aristoteles)

13. In de huisartsgeneeskunde is evidence belangrijk, maar ligt empirie aan de basis van de meeste dagelijkse beslissingen. (naar Stella Torn Broers, Siebolt van Dijk en anderen)

App-based treatment for female urinary incontinence

Evidence based eHealth as an alternative to care-as-usual

Anne Martina Maria Loohuis

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App-based treatment for female urinary incontinence

Evidence-based eHealth as an alternative to care-as-usual

Proefschrift

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Contents

PREFACE

The URinControl-study

This thesis is submitted in fulfilment of the requirements for a postgraduate doctorate qualification at the University of Groningen. The research is part of a larger study, the "URinControl-study", evaluating an app-based treatment for female urinary incontinence in primary care from multiple perspectives through a combination of methods. This thesis will focus on the perspectives of study design and participant recruitment in eHealth, effectiveness and cost-effectiveness of the app-based treatment and (personal) factors related to treatment success.

The research was conducted under the supervision of prof. dr. M.Y. Berger, dr. M.H. Blanker, dr. H. van der Worp and dr. J.H. Dekker of the Department of General Practice and Elderly Care Medicine at the University Medical Center Groningen. The research was performed in close cooperation with Nienke J. Wessels, also a general practice trainee and PhD-student within the URinControl-study. Her research focused on the experiences and expectations of stakeholders and usage patterns of the app-based treatment.

Laymen's information/ Informatie voor leken

Are you a lay? Just take a look! / Ben je een leek? Volg het proefschrift via de illustraties!
During the URinControl-study, extra emphasis was placed on research communication for the lay public. We believe this was important for three reasons; to give insight into the result of the funding, to raise attention for urinary incontinence as a condition and to facilitate optimal implementation of the URinControl-app. Therefore all studies within this thesis are supported by laymen's illustrations and the complete thesis is summarized by a laymen's illustration and video. All laymen's materials were published at the study website; www.urincontrol.nl.

Met illustraties en samenvattingen voor leken hebben we ingewikkelde onderzoekstaal begrijpelijk gemaakt. Dit vonden we belangrijk om drie redenen: (1) Om te laten zien wat we met het onderzoeksgeld hebben gedaan, (2) om het taboe rondom ongewild urineverlies te doorbreken én (3) om de URinControl-app onder de aandacht te brengen. Elke studie in dit proefschrift begint met zo'n illustratie. Aan het einde is er een samenvatting in de vorm van een illustratie. Daarnaast maakten we een lekenvideo. Dit is ook allemaal terug vinden op de website van het onderzoek; www.urincontrol.nl

CHAPTER 1

General introduction

GENERAL INTRODUCTION

Urinary incontinence (UI) affects 1 in 3 women and can dramatically affect their quality of life. Effective conservative management options do exist, yet various challenges complicate their feasibility in clinical practice. The growth in eHealth treatment offers a new tool that could address these challenges; indeed, over 100 apps are currently available for UI. Despite this plethora of resources, evidence on the effects of eHealth for UI had only recently been published at the start of this thesis.[1,2] Therefore, although UI and eHealth are considered to fit well, is this truly the case?

Urinary Incontinence: The Condition and Its Challenges

Urinary incontinence

UI, which refers to the involuntary loss of urine,[3] has three common subtypes: (1) stress UI, which refers to the loss of urine on effort or physical exertion, such as coughing or jumping on a trampoline; (2) urgency UI, which refers to the sudden need to urinate associated with a loss of urine; and (3) mixed UI, which is a combination of both stress and urgency UI. The involuntary loss of urine can negatively affect a woman's wellbeing by causing anxiety and lowering her quality of life.[4,5] This extends to problems related with pleasant social activities, like playing with children, going on a trip, or engaging in (sexual) relationships. Moreover, UI is a common disease that affects 25%–45% of women in the general population and has a prevalence that increases with age.[3] Whereas stress UI most often occurs in younger women, with the classic example being after giving birth, urgency and mixed UI most often occur in postmenopausal and older women.[6,7] In this latter domain, UI is one of the five "geriatric giants" described by Isaacs, representing a condition that causes significant disability and utilization of medical and social care in the elderly.[8]

Treatment for UI comprises general lifestyle advice (e.g., cutting down on coffee intake), general treatment (optimizing health and care), and type-specific treatment (e.g., medication and specific exercise).[3,9] General medication that can worsen UI should be reviewed (e.g., diuretics) and treatment for comorbidities that influence UI should be optimized (e.g., asthma, which causes coughing, or being overweight, which increases intra-abdominal pressure). Incontinence materials may need to be prescribed as supportive management. Concerning stress UI, pelvic floor muscle therapy (PFMT), pessaries, and mid-urethral slings show favorable effects, with 50%–75% of women cured and 66%–95% of women satisfied after treatment.[9,10] By contrast, urgency UI is treated by bladder training, PFMT, and/or anticholinergic medication, which improve symptoms in 90%, 73%, and 56%, respectively.[10-12]

Challenges in incontinence

Challenges related to the start (help-seeking), delivery (incomplete or suboptimal), and continuation (varying adherence) of treatment complicate the provision of good quality care for women with UI.

In the first instance, most women with UI (64%) do not seek help. They may consider their complaint to be minor, may have found a way to cope, or may believe that it is a normal and untreatable part of aging.[13,14] Research indicates that, among these women who do not seek help, some do want treatment.[15] When a women does take the step to seek help from a general practitioner (GP), the treatment prescribed and the required compliance are often suboptimal. The most frequent "intervention" by GPs is to prescribe incontinence pads, often without any active treatment.[16] GPs only refer 12% of their patients with UI to a physiotherapist and are reluctant to prescribe medication.[16,17] When a woman initiates bladder training or PFMT, the effectiveness of this treatment is highly dependent on adherence during the intervention and maintenance phases.[3,18] Unfortunately, compliance can be extremely variable, with "trouble remembering" cited as a major reason for low adherence in the long term.[19]

Together, these challenges can lead to needless suffering, inadequate healthcare provision, and unnecessary high personal and societal costs. In other somatic diseases, such as congestive heart failure (for support) and diabetes (for self-management), it has been shown that eHealth can address some of these challenges.[20] Therefore, could an eHealth strategy address these problems in UI?

Urinary Incontinence and eHealth

Can eHealth solve the problem of urinary incontinence?

eHealth interventions are tools or treatments delivered via internet or mobile platforms that typically seek to change behavior.[21] Their delivery via apps on smartphones has a huge potential to improve healthcare, not least because these are owned by most people, are convenient and easy to access, and can allow for personalized and interactive interventions at low costs.[22] An app-based treatment of female UI would benefit from these features, not only lowering barriers by offering anonymous and easily access but also increasing awareness through its wide availability.[2] Such treatment may also improve treatment delivery by independently guiding patients without requiring the input of a caregiver. With this technology, it is possible to personalize treatment based on targeted questions (e.g., defining the subtype of UI a woman has and providing advice on appropriate treatment). The app's availability can also improve treatment adherence by providing instant support on the execution of exercises and their integration in daily life. Some of these expected advantages have been mentioned by Swedish women using an internet-based treatment for UI.[2] Nevertheless, several doubts still persist because of the lack of support, with some

important questions arising. For example, are women who follow therapy on their own able to train correctly? Also, is self-training as effective as training supported by a caregiver? It should also be noted that we do not know whether all women will benefit from the advantages described above, or indeed, if app-based treatment is only suitable for a specific subset of woman.

eHealth (for urinary incontinence): Development on the loose

Given that there are already more than 100 apps available for UI in popular app-stores, many developers have clearly seen the potential of this tool. The government also sees a bright future for eHealth in general, encouraging its development by offering financial support to information technology specialists.[23,24] However, while the development of medical apps has been on the increase, there has been only limited control of development quality and limited evaluation of the medical effects through research. For example, only a few developers (15 of 131 apps) offered any background information when requested in an evaluation of apps available for UI in 2016, with the quality of development and evaluation reported to be very low.[24] In other research into new medical devices for UI promoted at scientific conferences, convincing evidence of their effectiveness was reported to be lacking despite many already being on the market.[25] The process for introducing these devices contrasts starkly with the strict requirements for introducing new drug classes. At the start of this research, no results on the effectiveness of an app-based treatment for UI had been published.

The implementation of eHealth also lags behind in terms of development and expectation according to the eHealth monitor of Nictiz.[26] Often, eHealth is not tailored to the requirements of the end-user, and neither its added value nor its effects are clear. For example, it is hard for a patient or GP to assess the quality and applicability of currently available apps for UI. A list has been produced to guide medical doctors through the process of assessing a medical app by addressing basic information, performance, and privacy.[27] However, even these data are often unavailable for many apps, the assessment itself is too time-consuming for use in clinical practice, and the assessment does not allow for quality to be compared with other apps or care-as-usual.

At present, there is a clear mismatch between the aims of developers (targeted at users, downloads and profits) and the needs of health professionals and patients (targeted at improving health and care outcomes).

Evidence-based eHealth: A Positive Effect Is Not Guaranteed

Government and developer stakeholders often emphasize the expected advantages of eHealth without also considering the possible harms and disadvantages. None has been studied for eHealth in the management of UI, yet several plausible issues exist. It is imaginable, for example, that a woman with overactive pelvic floor muscles may focus on strengthening instead of relaxation, potentially worsening their UI. Some apps imply that they offer treatment, yet they fail to provide content in line with approved guidelines for the treatment of UI (Appendix 1).[24] This could cause harm by distracting the patient from an existing, effective treatment.

An example of the potential for unsatisfactory outcomes has been reported in diabetes care, where research has shown that apps can put their users at serious health risks. In one study, 46 apps for calculating a short-acting insulin dose were assessed for input validation, correct dose calculation, and safety.[28] Only one app was deemed sufficient according to these criteria, with shocking evidence that the other apps put users at risk of both catastrophic overdose and more subtle harms from suboptimal glucose control. Considering the risks, it was concerning that 105,000 patients worldwide had downloaded an app included in this study.

Proper evaluation of an app's components is needed to ensure a high quality of care and implementation. Relevant questions include the following: what are the effectiveness and cost-effectiveness of the app in comparison to the current best treatment? For whom does the app work best? How does the app work? And, what are the expectations and experiences of end-users?

No gold standard exists for proper evaluation of eHealth, but some generally accepted views do exist on how this should take place.[29] These considerations are in line with the framework for assessing a complex intervention set out by the Medical Research Counsel,[30] arguing that methods should follow the research question and that no single study design alone can answer all questions related to app-based treatment. Evaluation should take place in several development phases that combine multiple methods: a randomized controlled trial is suited to answer questions about the impact on patient outcomes and costs; interviews and focus-group sessions give insights into experiences and expectations; facilitators and barriers can be identified by combining these methods; and log-data analysis can be used to understand app usage.

Research is expensive and takes time, but as researchers, developers, and healthcare professionals, it is our responsibility to offer patients the best current treatment. Therefore, in the first instance, we must compare new treatments to existing ones properly because we cannot assume that eHealth will have a positive effect on outcomes.

This Thesis

An app-based treatment for UI could offer a new treatment strategy to address help-seeking behavior, treatment delivery, and treatment adherence/continuation. However, we are currently in a phase where development has been outpacing proper evaluation and implementation. In this thesis, the overall aim is therefore to assess if, and for whom, an app-based treatment for female stress, urgency, and mixed UI is a suitable alternative to care-as-usual in general practice. To evaluate a complex intervention like app-based treatment properly, the methods needed to address each question required consideration. This resulted in a mixed-methods study design (Chapter 2).

The various elements of the study are then described in Chapters 3 through 7. The laborious process of participant recruitment by GP's and the evaluation of an alternative recruitment strategy through (social) media is reported in Chapter 3. However, the most important question, whether app-based treatment works, is answered in Chapters 4 and 5 where the effectiveness and cost-effectiveness of app-based treatment are compared to care-as-usual in the short and long term. For optimal implementation, it is necessary to understand for whom and how the app-based treatment works. To this end, Chapter 6 summarizes the development of a prediction model that uses a personalized advantage index to facilitate informed choice between app-based treatment and care-as-usual. Finally, the facilitators and barriers related to treatment success are considered in Chapter 7.

The general discussion (Chapter 8) reflects on these findings considering the methodological challenges of evidence-based eHealth in general and the current state of evidence-based eHealth for UI, the clinical implications and societal impact of the present research, together with the potential targets and needs of future research.

REFERENCES

1. Sjöström M, Umefjord G, Stenlund H, Carlbring P, Andersson G, Samuelsson E. Internet-based treatment of stress urinary incontinence: 1- and 2-year results of a randomized controlled trial with a focus on pelvic floor muscle training. Brit J Urol Intl [Internet]. 2015 Dec [cited 2019 Feb 1];116(6):955–64. Available from: http://doi.wiley.com/10.1111/bju.13091
2. Björk AB, Sjöström M, Johansson EE, Samuelsson E, Umefjord G. Women's experiences of internet-based or postal treatment for stress urinary incontinence. Qual Health Res. 2014;
3. Abrams P, Andersson K-E, Apostolidis A, Birder L, Bliss D, Brubaker L, et al. 6th International Consultation on Incontinence. Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence. Neurourol Urodyn. 2018 Sep;37(7):2271–2.
4. Coyne KS, Kvasz M, Ireland AM, Milsom I, Kopp ZS, Chapple CR. Urinary incontinence and its relationship to mental health and health-related quality of life in men and women in Sweden, the United Kingdom, and the United States. Eur Urol. 2012;61(1):88–95.
5. Nilsson M, Lalos O, Lindkvist H, Lalos A. How do urinary incontinence and urgency affect women's sexual life? Acta Obstet Gynecol Scand. 2011;90(6):621–8.
6. Melville JL, Katon W, Delaney K, Newton K. Urinary incontinence in US women: A population-based study. Arch Intern Med. 2005;165(5):537–42.
7. Lagro-Janssen A. Urine-incontinentie bij vrouwen in de huisartspraktijk. Katholieke Universiteit Nijmegen; 1991.
8. Isaacs B. An introduction to geriatrics. Bailliere, Tindall & Cassell; 1965. 224 p.
9. Damen-van Beek Z, Wiersma T. Practice guideline 'Urinary incontinence in women' from the Dutch College of General Practitioners. Ned Tijdschr Geneeskd. 2016;160:D674.
10. Dumoulin C, Cacciari LP, Hay-Smith EJC. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database of Systematic Reviews. 2018.
11. Wallace SA, Roe B, Williams K PM. Bladder Training for Urinary Incontinence in Adults. Cochrane Database Syst Rev. 2004;(1).
12. Shamliyan T, Wyman JF, Ramakrishnan R, Sainfort F, Kane RL. Benefits and Harms of Pharmacologic Treatment for Urinary Incontinence in Women A Systematic Review [Internet]. [cited 2020 Nov 10]. Available from: www.annals.org
13. Visser E, De Bock GH, Kollen BJ, Meijerink M, Berger MY, Dekker JH. Systematic screening for urinary incontinence in older women: Who could benefit from it? Vol. 30, Scandinavian Journal of Primary Health Care. 2012. p. 21–8.
14. Teunissen D, van Weel C, Lagro-Janssen T. Urinary incontinence in older people living in the community: Examining help-seeking behaviour. Br J Gen Pract [Internet]. 2005 Oct [cited 2020 Nov 10];55(519):776–82. Available from: /pmc/articles/PMC1562332/?report=abstract
15. Visser E, De Bock GH, Messelink EJ, Schram AJ, Kollen BJ, Van Gemert SLB, et al. Active encouragement of older women with urinary incontinence inprimary care to undergo diagnosis and treatment: A matched-paircluster randomized controlled trial. Maturitas. 2015 Feb 1;80(2):212–9.
16. Van Gerwen MAG, Schellevis FG, Lagro-Janssen ALM. Management of urinary incontinence in general practice: Data from the second Dutch national survey. J Eval Clin Pract. 2009;15(2):341–5.
17. Minassian VA, Yan X, Lichtenfeld MJ, Sun H, Stewart WF. The iceberg of health care utilization in women with urinary incontinence. Int Urogynecol J. 2012;23:1087–93.

18. Lagro-Janssen T, Van Weel C. Long-term effect of treatment of female incontinence in general practice. Br J Gen Pract. 1998;48(436):1735–8.

19. Borello-France D, Burgio KL, Goode PS, Ye W, Weidner AC, Lukacz ES, et al. Adherence to Behavioral Interventions for Stress Incontinence: Rates, Barriers, and Predictors. Phys Ther [Internet]. 2013 Jun 1 [cited 2020 Nov 10];93(6):757–73. Available from: https://academic.oup.com/ptj/article/93/6/757/2735358

20. Elbert NJ, Van Os-Medendorp H, Van Renselaar W, Ekeland AG, Hakkaart-Van Roijen L, Raat H, et al. Effectiveness and cost-effectiveness of ehealth interventions in somatic diseases: A systematic review of systematic reviews and meta-analyses. Vol. 16, Journal of Medical Internet Research. Journal of Medical Internet Research; 2014.

21. Eysenbach G, Group C. CONSORT-EHEALTH: Improving and Standardizing Evaluation Reports of Web-based and Mobile Health Interventions. J Med Internet Res [Internet]. 2011 [cited 2019 Jan 2];13(4):e126. Available from: http://www.jmir.org/2011/4/e126/

22. Free C, Phillips G, Watson L, Galli L, Felix L, Edwards P, et al. The Effectiveness of Mobile-Health Technologies to Improve Health Care Service Delivery Processes: A Systematic Review and Meta-Analysis. PLoS Med. 2013;10(1).

23. Rijksoverheid. Zorgvoorinnoveren/ Financiele ondersteuning [Internet]. [cited 2021 Feb 18]. Available from: https://www.zorgvoorinnoveren.nl/financiele-ondersteuning

24. Loohuis A, Chavannes N. Medical apps; Care for the future? [Dutch]. Huisarts Wet. 2017;60:440–3.

25. te Brummelstroete GH, Loohuis AM, Wessels NJ, Westers HC, van Summeren JJGT, Blanker MH. Scientific evidence for pelvic floor devices presented at conferences: An overview. Neurourol Urodyn. 2019;38(7).

26. Nictiz & Nivel. Meer dan techniek. Ehealth -Monitor 2016. 2016;180.

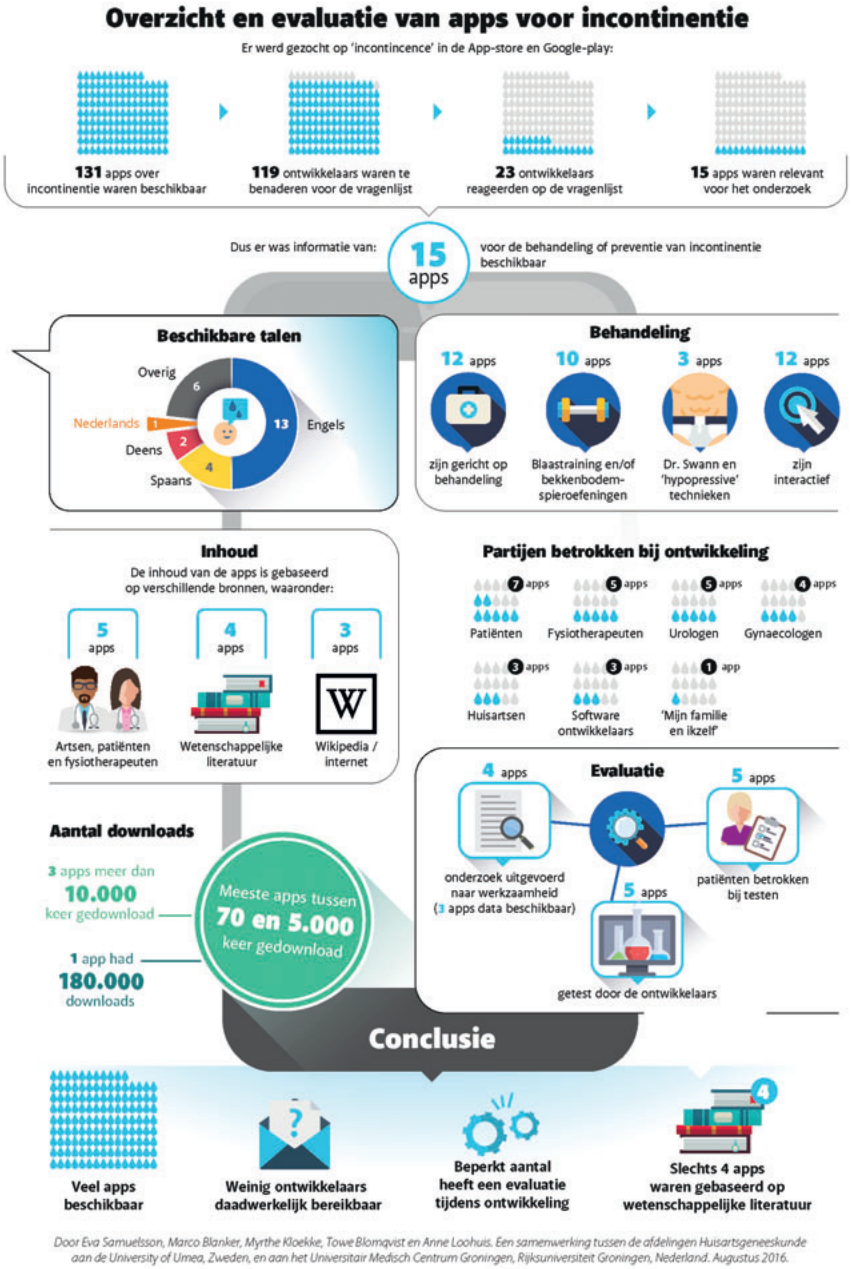
27. KNMG. Medische App Checker : beoordeling van medische apps. 2016;1–20.

28. Huckvale K, Adomaviciute S, Prieto JT, Leow MKS, Car J. Smartphone apps for calculating insulin dose: A systematic assessment. BMC Med. 2015;13(1):1–10.

29. Liu JLY, Wyatt JC. The case for randomized controlled trials to assess the impact of clinical information systems. J Am Med Informatics Assoc. 2011;18(2):173–80.

30. Craig P, Dieppe P, Macintyre S, Mitchie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: The new Medical Research Council guidance. Bmj [Internet]. 2008;337(7676):979–83. Available from: http://dx.doi.org/doi:10.1136/bmj.a1655

Appendix 1 Dutch infographic; development and evaluation of available apps for urinary incontinence. Part of publication: *Loohuis A, Chavannes N. Medical apps; Care for the future? [Dutch]. Huisarts Wet. 2017;60:440–3.*



CHAPTER 2

The impact of a mobile application-based treatment for urinary incontinence in adult women: Design of a mixed-methods randomized controlled trial in a primary care setting

Neurourology and Urodynamics. 2018: 1-10.

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**Shared authorship*


Onderzoeksdesign
URINCONTROL ONDERZOEK
Idee
APP
therapietrouw
24/7
toegankelijkheid
behandeleffect
kosten
vraag
Is appbehandeling een alternatief voor standaard zorg?
aanleiding
1 op de 3 vrouwen ongewild urineverlies
Neurourol. Urodyn 2018
vergelijkend onderzoek
IK HELP JE
onderzoek
Interviews
focusgroepen
logdata
VISUALPOWEROSO

ABSTRACT

Aims: We aim to assess whether a purpose-developed mobile application (app) is non-inferior regarding effectiveness and cost-effective when used to treat women with urinary incontinence (UI), as compared to care as usual in Dutch primary care. Additionally, we will explore the expectations and experiences of patients and care providers regarding app usage.

Methods: A mixed-methods study will be performed, combining a pragmatic, randomized-controlled, non-inferiority trial with an extensive process evaluation. Women aged ≥18 years, suffering from UI ≥ 2 times per week and with access to a smartphone or tablet are eligible to participate. The primary outcome will be the change in UI symptom scores at 4 months after randomization, as assessed by the International Consultation on Incontinence Modular Questionnaire UI Short Form. Secondary outcomes will be the change in UI symptom scores at 12 months, as well as the patient-reported global impression of improvement, quality of life, change in sexual functioning, UI episodes per day, and costs at 4 and 12 months. In parallel, we will perform an extensive process evaluation to assess the expectations and experiences of patients and care providers regarding app usage, making use of interviews, focus group sessions, and log data analysis.

Conclusion: This study will assess both the effectiveness and cost-effectiveness of app-based treatment for UI. The combination with the process evaluation, which will be performed in parallel, should also give valuable insights into the contextual factors that influence the effectiveness of such a treatment.

BACKGROUND

eHealth, which represents health services and information delivered or enhanced through the internet and related technologies, is an emerging clinical resource with potential advantages for the treatment of urinary incontinence (UI).[1] In particular, the use of mobile health applications (apps) may increase adherence to treatment advice and thereby reduce costs.[2] Although conservative treatment is effective for UI, adherence varies from 18% to 95% and is one of the main problems in the treatment of UI.[3] Also, total costs for absorbent materials, pelvic physiotherapy, medication and specialist care are high.[4] Currently, various apps have been designed to support the treatment of UI, but research on their effectiveness, quality, and usability is scarce.

Recently, the use of an app-based treatment for stress UI was assessed in Swedish women in a community setting, and not only produced clinically relevant symptom improvement but also reduced pad usage compared with postponed treatment.[5] In other research, an internet-based training program was shown to be a cost-effective alternative for treating stress UI when compared with a treatment program sent by post.[6] However, studies evaluating app-based treatment for all three types of UI (i.e., stress, urgency, and mixed UI) are lacking, and app-based treatment for UI has never been compared to care as usual. Moreover, there is a lack of research into the experiences and preferences of important stakeholders, such as patients and care providers, which can often result in poor implementation of such eHealth solutions.[7]

Therefore, using a mixed-methods study design, we will evaluate an app-based treatment for stress, urgency, and mixed UI in women. Our aims in this study are two-fold: first, we will assess whether a purpose-developed app is non-inferior and cost-effective in treating women with UI, as compared to care as usual in Dutch primary care; second, we will evaluate the expectations and experiences of patients and care providers regarding use of the app. By combining these results, we expect to provide valuable insights into the facilitators of, and barriers to favorable outcomes for mobile app use in the treatment of UI.

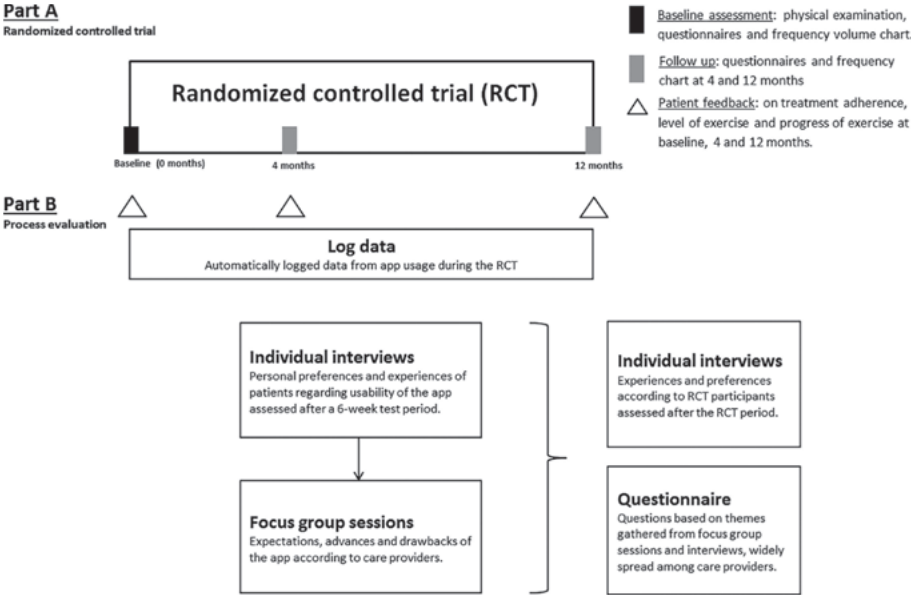
METHODS

Study Design

In this mixed-methods study, a pragmatic, randomized-controlled, non-inferiority trial will be conducted in parallel with a process evaluation study (Figure 1). The randomized-controlled trial (RCT; Part A) is designed to study the non-inferiority and cost-effectiveness of an app-based treatment for UI, compared to care as usual in primary care.

We have chosen a pragmatic design because we want to provide the best reflection of the expected effect of the intervention under real-life conditions. We opted for non-inferiority because we wanted to show that the intervention is not less effective than the established treatment. This approach is recommended in light of the fact that eHealth interventions may offer additional advantages.[8] We hypothesize that app-based treatment for women with incontinence will not be less effective than care as usual in primary care, and that it will increase the cost-effectiveness of treatment by reducing the need for face-to-face consultations with care providers such as general practitioners (GP) and pelvic physiotherapists. In the process evaluation (Part B), we aim to assess the experiences and expectations of patients and healthcare professionals regarding the use and implementation of the new app.

Figure H2.1. An overview of the mixed-methods for the URinControl study design.



Part A shows the RCT with details of the planned baseline assessment and follow-up assessments at 4 and 12 months. Part B shows the planned process evaluation that will be conducted parallel to the RCT, and that will collect app usage data, patient feedback, patient interviews, focus group sessions and a questionnaire for care providers. Results from the usability study with patients and the focus group sessions will be used to develop a quantitative questionnaire and form an interview guide for a qualitative evaluation within the RCT.

The RCT is registered in the Dutch Trial Register (registration number NTR21609), approval was obtained from the Medical Ethical Review board of the University Medical Center Groningen (UMCG), the Netherlands (METc-number: 2014/574). The Medical Research Involving Human Subjects Act (WMO) does not apply for the process evaluation, which has been confirmed by the Medical Ethical Review board of the UMCG (letter-number: M17.207954).

Part A: The RCT

Setting

Participants will be recruited in the northern part of the Netherlands. Recruitment has started in October 2015 through primary care practices. Additionally, as from November 2017, participants are also recruited through lay press and social media attention and through the study website.

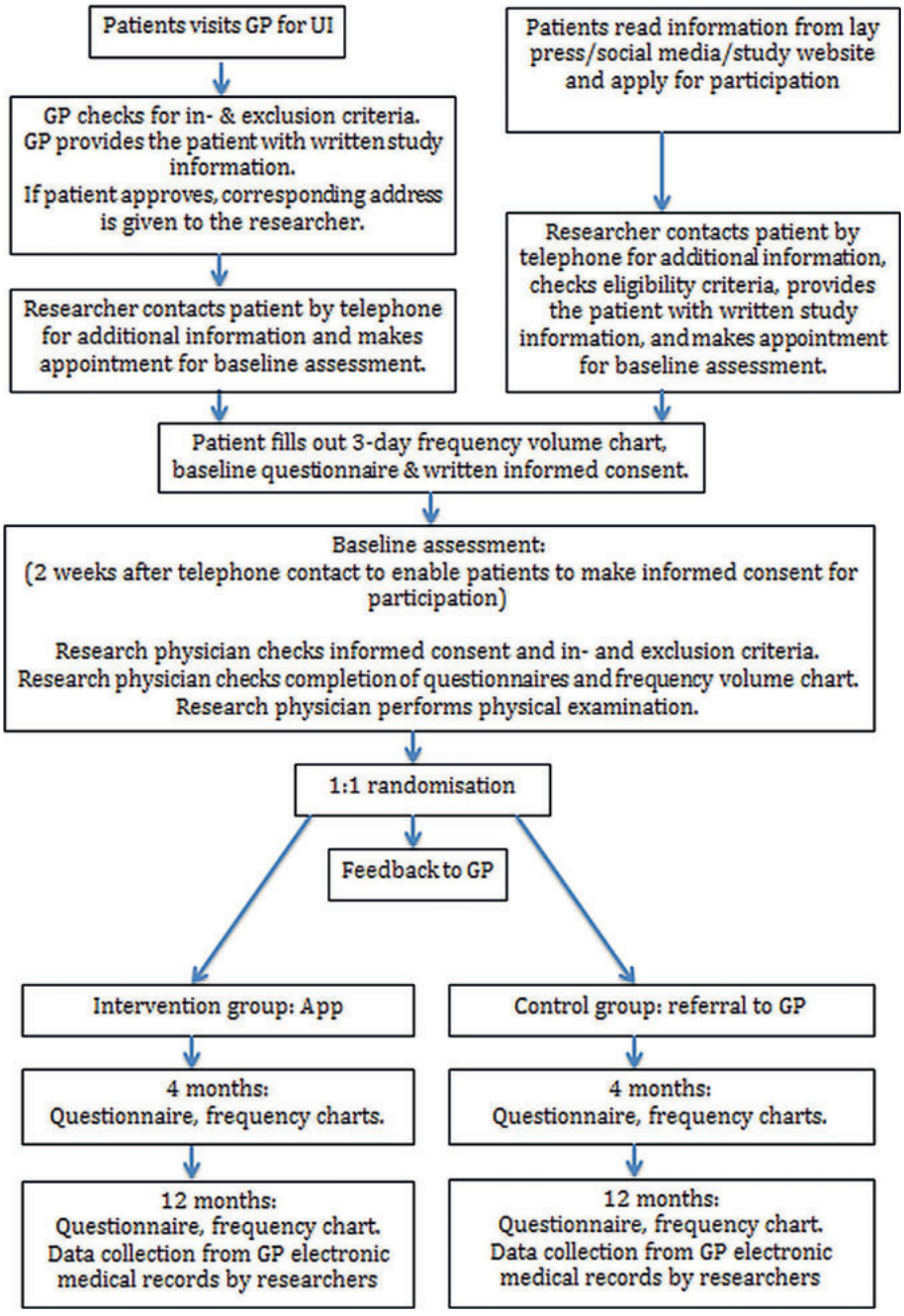
Recruitment of participants

The process for participant recruitment is shown in Figure 2. We will use the following inclusion criteria: female sex; age ≥18 years; self-reported stress, urgency, or mixed UI at least twice a week according to the Three Incontinence Questions (3IQ, Appendix 2); wanting treatment; and access to a smartphone or tablet. Women are excluded in case of: indwelling urinary catheter, urogenital malignancy, previous surgery for UI, treatment for UI in the previous year (pharmacological or non-pharmacological), terminal or serious illness, cognitive impairment or psychiatric illness, urinary tract infection (UTI) (dipstick, and if negative, dipslide or urine culture), overflow or continuous UI, pregnancy or recent childbirth (<6 months ago) or the inability to complete a questionnaire in Dutch. Eligibility is assessed by the patient's GP or by the research physician based on a patient history. As from November 2017, urinalyses will only be performed in case of clinical suspicion of a UTI. Eligible women will be invited to participate with an information letter. Informed consent will be obtained by the researcher during baseline assessment.

Randomization

After baseline assessment the researcher will randomize the participants using the validated web-based computer program ALEA.[9] Block randomization with random block sizes will be applied at the GP level to correct for differences between GPs.

Figure H2.2. Flowchart of patient inclusion and assessments in the randomized-controlled trial (Part A)



Abbreviations: GP, general practitioner; UI, urinary incontinence

Interventions

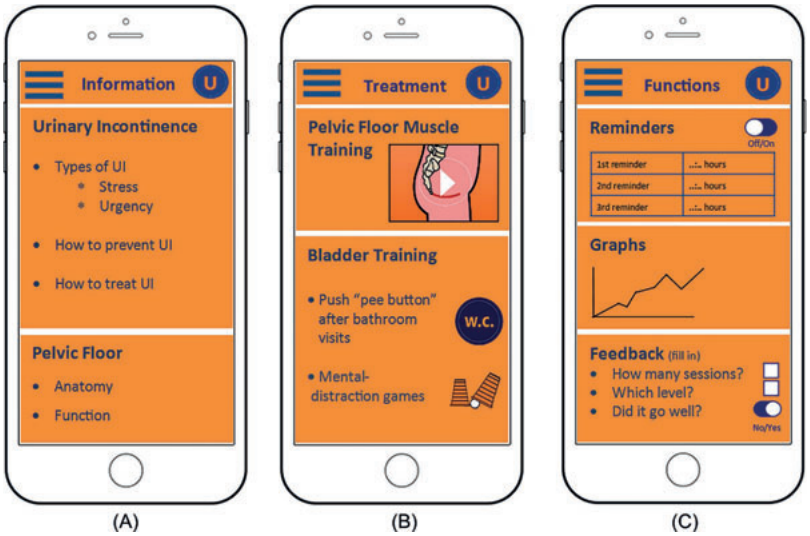
The URinControl App

Participants in the intervention group will have access to a smartphone or tablet app, which we named the URinControl App. This contains a step-by-step program for the treatment of each type of UI, mainly focusing on pelvic floor muscle and/or bladder training depending on the primary diagnosis (Figure 3). The app will guide participants to the appropriate part of the app, to start directed training, and, if applicable, when to add the other type of training. Participants in the intervention arm will be asked to use the application as a self-management tool without caregiver involvement. The research team will only provide technical support, but the participant will be free to contact her GP regarding any questions regarding the medical aspects of her condition or treatment. The GP can then decide what additional support is needed, if any.

Care as usual (control group)

Participants in the control group will receive treatment according to the Dutch GP guideline on UI.[10] They will be referred back to their GP who will discuss the various treatment options. The management plan can then vary depending on the preferences of patients and GPs, but may involve any of the following: instructions on pelvic floor muscle and/or bladder training; prescribing a pessary, drugs, or absorbent products; or referral to a continence nurse, a pelvic physiotherapist, or to secondary care (i.e., a urologist/gynecologist). Due to the pragmatic nature of this trial, referred patients will be treated according to current guidelines in these settings. Detailed information on the applied treatments will be collected.

Figure H2.3. A schematic representation of the contents of the URinControl App



(a) Information on both types of urinary incontinence, prevention and treatment options, as well as information on anatomy and function of the pelvic floor.
(b) Training programs for both stress and urgency urinary incontinence (pelvic floor muscle training and bladder training, respectively).
(c) Functionalities of the App, including three reminder-options, the graph function, and a patient feedback option.

Measurements

Baseline assessment

History and physical examination

After gaining informed consent, a research physician will assess age, parity, UI duration, comorbidity and drug use, and will measure the participant's weight and height, and perform a baseline urogynecological assessment. Pelvic floor muscle function will be assessed according to recommendations of the International Continence Society, and the stage of pelvic organ prolapse will be assessed using the Pelvic Organ Prolapse Quantification (POP-Q) method.[11,12]

Questionnaires

Participants will complete validated questionnaires on UI symptoms (the International Consultation on Incontinence Modular Questionnaire UI Short Form, ICIQ-UI-SF); condition-specific (ICIQ-LUTS-QoL) and generic health-related (EuroQol questionnaire, EQ-5D-5L) quality of life; and the influence of incontinence on sexuality (Pelvic Organ

Prolapse/Incontinence Sexual Questionnaire, International Urogynecological Association-revised: PISQ-IR). Finally, a question on the use of absorbent pads and UI-specific healthcare will be added to the questionnaire set (Appendix 2).

Frequency volume chart

Participants will complete a three-day frequency volume chart that will be used to gain insight into the frequency of micturition, number of UI episodes, and volumes of urine voided per micturition.

Follow-up assessment

At 4 and 12 months, all baseline questionnaires will be repeated. Participants will also complete a frequency chart (without volume measurements). Additionally, the Patient Global Impression of Improvement (PGI-I), for both incontinence and sexuality, will be administered. All medical cost items related to UI will be measured with the adjusted versions of the Institute of Medical Technology Assessment Medical Consumption Questionnaire (iMTA-MCQ) and the Productivity Costs Questionnaire (iMTA-PCQ). After 12 months, data from the electronic medical records of GPs will be collected retrospectively to assess UI-specific costs, including that related to referrals, consultations with healthcare professionals, prescribed medication and absorbent pads, and UI-associated comorbidity.

App usage

We will monitor App usage by two types of data; data filled in by the participant and automatically logged data. Participants are invited to fill in whether they performed their exercises, at what level and if it went well. Actual activity is automatically logged; e.g. data on opening/closing different exercise levels and duration of use.

Primary outcome

The primary outcome of interest is the change in UI symptoms score assessed by the ICIQ-UI-SF at 4 months after randomization.

Secondary outcomes

The secondary outcomes are as follows:

- Severity of UI (measured with the ICIQ-UI-SF) at 12 months.
- Patient's global impression of improvement (PGI-I) on UI and sexuality at 4 and 12 months.
- Condition-specific quality of life (assessed with the ICIQ-LUTS-QoL) at 4 and 12 months.
- Generic health-related quality of life (assessed with the EQ5D-5L) at 4 and 12 months.
- Condition-specific sexual functioning (assessed with the PISQ-IR) at 4 and 12 months.
- Number of UI episodes per day (derived from frequency charts) at 4 and 12 months.
- Costs at 4 and 12 months, measured with the adjusted iMTA-MCQ and iMTA-PCQ, and extracted from electronic medical records after 12 months.

Blinding

Due to the nature of the interventions, blinding for treatment allocation is not feasible.

Sample size

We have opted for a non-inferiority design, which means that the sample size calculation is based on the hypothesis that the app-based treatment group will be inferior to the care as usual group (H0 hypothesis). Rejection of this hypothesis leads to acceptance of non-inferiority (H1 hypothesis). One recent study, using anchor-based methods to determine the minimal clinically important difference (MCID), identified a between-treatment MCID of 1.58 points among patients with stress UI.[13] We therefore based the sample size calculation on an estimated non-inferiority margin of 1.5 points, a one-sided type I error of 0.025, and a power of 0.80. This generated a total requirement of 100 evaluable patients per group. Allowing for an expected loss-to-follow-up of up to 20%, we will require 250 patients for this study. We aim to have 90 participating GP's, who should include 2,5 patients each. We expect this to be achievable, since the incidence of UI in primary practice is 9.3 per 1000 patient years.[14]

Analysis

Descriptive analyses

We will describe frequencies of stress, urgency, and mixed UI for the intervention and control groups, including analysis by age distribution, educational level, previous smartphone and/or tablet experience, recruitment strategy, and baseline questionnaire scores.

Analyses of clinical outcomes

A linear regression model will be used for non-inferiority testing, with adjustment for confounders if necessary. In case of non-inferiority, we will assess superiority with a two-sided test, using a significance level of $p < 0.05$. A missing value analysis will be performed and multiple imputation techniques will be used, as appropriate.

There is no gold-standard analysis in non-inferiority trials. Intention-to-treat (ITT) analyses, risk bias toward the null hypothesis.[15] However, the alternative per-protocol (PP) analysis can cause bias in either direction by allowing patients to be excluded.[15] Therefore, both ITT and PP analyses will be performed in this study.

Analysis of cost data

In the economic evaluation, the primary aim will be to estimate the societal costs of women with UI using an interactive app compared with the costs of care as usual following established guidance. Such a societal perspective incorporates direct and indirect healthcare costs, such as direct medical costs, patient and family costs, and costs due to productivity losses.[16]

A cost-effectiveness analysis (CEA) will also be performed from a societal perspective. We will use the incremental cost-effectiveness ratio (ICER) as a composite outcome score. The ICER will indicate the ratio of additional costs or gains of treatment based on using the app, as well as the additional change in symptom score measured with the ICIQ-UI-SF, compared to care as usual. We will also perform a cost-utility analysis based on EuroQol 5D-5L defined utilities.[17]

Part B: Process Evaluation

Process evaluations can improve the validity and outcome interpretation of RCTs to help refine an intervention.[18] We therefore aim to conduct an extensive process evaluation to answer two research questions:

1. What are the experiences and expectations of patients and care providers regarding the use and implementation of our app-based management of UI?
2. What is associated with success or failure of the app-based management of UI?

To answer the first research question, we will conduct a usability study. To avoid influencing the RCT, we will recruit women who meet the inclusion criteria, but who do not participate in the RCT. Participants will be asked to use the URinControl App for 6 weeks, after which semi-structured interviews will be conducted to assess usability preferences and experiences. Additionally, focus group sessions will be held with relevant occupational groups (e.g., GPs, practice assistants, pelvic physical therapists, and urogynecologists) and supplemented with one multidisciplinary focus group session. Results from the usability study will be used to provide additional input for these sessions. Focus group sessions will be exploratory in nature, so participants with a range of characteristics will be invited from local health facilities. Finally, the results from the usability study and focus group sessions will be used to develop a quantitative questionnaire that will be distributed among health professionals in the Netherlands to assess their opinions on the themes collected. This should provide a deeper understanding of the context in which future implementation of an app for UI should take place.

To answer the second research question, we will integrate the results of automatically logged usage data (log data) analysis, patient interviews, and quantitative results of the RCT. Log data will be gathered from the apps to provide a more in-depth insight into adherence.[19] After 12 months' follow-up, patient interviews will be held, aiming to include approximately 40 participants from the RCT. The results from the previously described focus group sessions and usability study will be used to form an interview guide for this qualitative evaluation within the RCT. Additionally, during the RCT, participants will be asked to answer open-ended questions at baseline and follow-up regarding their personal view on the success or failure of treatment. By integrating these results with quantitative results of the RCT, we aim to provide greater insight into the facilitators of, and barriers to, treatment success with the URinControl App.

Analysis

The semi-structured interviews and focus group sessions will be recorded using a digital voice recorder and transcribed verbatim. Transcriptions will be coded using the Atlas.ti (Scientific Software Development program). Coding will be performed separately by two researchers and checked for agreement. Data analysis will be driven by an inductive approach, allowing themes to emerge from the data by constant comparison.

Sample size

Participants will continue to be enrolled for individual interviews until no new themes emerge from the data (i.e., saturation is reached).[20] The focus groups will be performed with care providers and consist of 6–8 people per session.

DISCUSSION

This study will evaluate an app-based treatment of UI for women in primary care, using a mixed-methods design. The non-inferiority to care as usual, the cost-effectiveness, and the expectations and experiences of stakeholders will be evaluated. Ultimately, the study aims to provide more insight into the processes underlying the use and effectiveness of an app for managing UI, which should help to improve the development and implementation of this and future eHealth tools.

To the best of our knowledge this is the first proposal that seeks to evaluate an eHealth-treatment for stress, urgency, and mixed UI, and it is the first that aims to do so in a help-seeking population in primary care. Only two previous studies have assessed internet- and/or app-based treatment for stress UI. These studies differ from ours in terms of treatment comparison (either a group receiving postal information or a group receiving postponed treatment, rather than comparison to usual care).[5,6]

The main strength of this study will be in the combination of research methods used. A mixed-methods study design is frequently used in social science and can make an important contribution to RCTs evaluating health service interventions.[21] In our design, the quality of the process evaluation has been strengthened by applying the three methods described by Zhang et al., namely the integration of quantitative with qualitative data, connecting portions of the study in phases, and embedding a parallel conducted qualitative assessment alongside an RCT.[22] Other strengths are the use of a non-inferiority design, the evaluation of experiences of both patients and professionals throughout the process, the societal cost-effectiveness evaluation, and the use of log data analyses. The use of pragmatic effectiveness analyses will provide a realistic comparison between care as usual and app-based treatment, and the use of log data from the app will provide valuable information on actual app use, progress, and adherence. Together, this information is essential to anticipate whether implementation will improve healthcare outcomes.

Potential challenges lie in participant recruitment, notably because there are well-known barriers to women seeking help for UI.[23] Another possible limitation may lie in the use of a pragmatic design; indeed, the features that support the generalizability of the results to real-world practice may also limit the interpretation of the results.[24] These features include the lack of blinding and possible sub-optimal adherence to therapy. Research within eHealth is relatively young, and there is no gold-standard process for conducting a process evaluation in this field.

We believe that this study is unique in combining several current guidelines on study design with advice regarding process evaluation, both in general and within eHealth specifically.[7,18,25] Therefore, this study design offers a multifaceted evaluation of an app-based eHealth intervention.

FUTURE PERSPECTIVES

Although eHealth is a promising and emerging technology, urogynecology apps have not been adequately tested or compared to care as usual. Moreover, experiences and preferences of important stakeholders are often not explored, resulting in poor implementation.[7] The results of this study will provide valuable insights into the contextual factors that influence the effectiveness of a mobile app in the treatment of UI and will provide useful information for the development and evaluation of future eHealth applications. If successful, the URinControl App will be made openly available for patients and health professionals, providing an easily accessible treatment option for women who experience barriers to asking for care.

REFERENCES

1. Eysenbach G. Wat is eHealth? J Med Internet Res. 2001;(Apr-Jun):3(2): e20.
2. Hamine S, Gerth-Guyette E, Faulx D, Green BB, Ginsburg AS. Impact of mHealth chronic disease management on treatment adherence and patient outcomes: A systematic review. J Med Internet Res. 2015;17(2):e52.
3. Dumoulin C, Hay-Smith EJC, Mac Habée-Séguin G. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2010;(1):Art. No.: CD005654.
4. http://www.rijksoverheid.nl/documenten-en-publicaties/rapporten/2013/04/25/technische-rapportage-ziektelast.html.
5. Asklund I, Nyström E, Sjöström M, Umefjord G, Stenlund H, Samuelsson E. Mobile app for treatment of stress urinary incontinence: A randomized controlled trial. Neurourol Urodyn. 2016;(August):1-8.
6. Sjöström M, Umefjord G, Stenlund H, Carlbring P, Andersson G, Samuelsson E. Internet-based treatment of stress urinary incontinence: 1- and 2-year results of a randomized controlled trial with a focus on pelvic floor muscle training. BJU Int. 2015;116(6):955-964.
7. Ossebaard HC, Van Gemert-Pijnen L. eHealth and quality in health care: implementation time. Int J Qual Heal Care. 2016;28(3):415-419.
8. Kummervold PE, Johnsen JAK, Skrøvseth SO, Wynn R. Using noninferiority tests to evaluate telemedicine and e-health services: Systematic review. J Med Internet Res. 2012;14(5):e132.
9. ALEA software for randomization in clinical trials. http://tenalea.net/Documents/ALEA/ALEARandomisationProgramFeatures.pdf.
10. Damen-van Beek Z, Wiersma T. Practice guideline "Urinary incontinence in women" from the Dutch College of General Practitioners. Ned Tijdschr Geneeskd. 2016;160:D674.
11. Messelink B, Benson T, Berghmans B, et al. Standardization of terminology of pelvic floor muscle function and dysfunction: Report from the pelvic floor clinical assessment group of the International Continence Society. Neurourol Urodyn. 2005;24(4):374-380.
12. Bump RC, Mattiasson A, Bo K, Brubaker LP, DeLancey JO KP. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obs Gynecol. 1996;175(1):10-.
13. Nyström E, Sjöström M, Stenlund H, Samuelsson E. ICIQ Symptom and Quality of Life Instruments Measure Clinically Relevant Improvements in Women With Stress Urinary. Neurourol Urodyn. 2015;34(3):747-751.
14. https://www.nivel.nl/nl/NZR/incidenties-en-prevalenties.
15. Rehal S, Morris TP, Fielding K, Carpenter JR, Phillips PPJ. Non-inferiority trials: are they inferior? A systematic review of reporting in major medical journals. BMJ Open. 2016;6(10):e012594.
16. Drummond MF, Stoddart GL, Torrance GW, Sculpher MJ, Claxton K. Methods for the economic evaluation of health care programmes (2015). Oxford Univ Press.
17. Versteegh, MM, Vermeulen KM, Evers S, de Wit A, Prenger R SE. Dutch tariff for the 5 level version of EQ-5D. Value Heal. 2016;19(4):p343–352.
18. Hulscher MEJL, Laurant MGH, Grol RPTM. Process evaluation on quality improvement interventions. Qual Saf Health Care. 2003;12(1):40-46.
19. Sieverink F, Kelders SM, Braakman-Jansen LMA, Van Gemert-Pijnen JEWC. The added value of log file analyses of the use of a personal health record for patients with type 2 diabetes mellitus: Preliminary results. J Diabetes Sci Technol. 2014;8(2):247-255.
20. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research. 2007;19(6):349-357.

21. Caffery LJ, Martin-Khan M, Wade V. Mixed methods for telehealth research. J Telemed Telecare. 2016:Epub ahead of print.
22. Zhang W, Creswell J. The use of "mixing" procedure of mixed methods in health services research. Med Care. 2013;51(8):e51-e57.
23. Visser E, de Bock GH, Kollen BJ, Meijerink M, Berger MY, Dekker JH. Systematic screening for urinary incontinence in older women: who could benefit from it? Scand J Prim Heal Care. 2012;30(1):21-28.
24. Ford I, Norrie J. Pragmatic Trials. N Engl J Med. 2016;375(5):454-463.
25. Kidholm K, Rasmussen J, Ekeland AG, et al. MethoTelemed - Final Study Report: Methodology to assess telemedicine applications. 2010.

APPENDICES

Appendix 1

URinControl App: contents and development

Main objectives

The program content is a translation of the recommendations of the guidelines on the treatment of female UI in primary care.[10] Development of the URinControl App was based on the following objectives: 1) to inform and educate the patient about UI; 2) to guide the patient through the main treatment exercises, without the need of instruction from a healthcare professional; 3) to increase adherence to exercises by integrating them in daily life; and 4) to give the patient insight into treatment progress (number and level of exercises performed over time). An overview of the contents of the URinControl App is shown in Figure 3.

Development and technical information

Members of the research project and its advisors, including physicians, pelvic physiotherapists, and patients, collaborated to develop the URinControl App program. The eHealth developers are experienced in the development of internet-based medical programs, and the program has been built on a secure platform, using a Secure Sockets Layer. During the study, the app will be exclusively available on the iOS™ (version 8.1) and Android™ (version 2.3.3) platforms through Therapieland B.V. (version 1.30 and 1.3), for patients in the intervention group. A pilot study was performed with patients suffering from UI to detect any irregularities and to review user-friendliness. Security and user-friendliness were also reviewed and approved by the committee of Medical Tools of the University Medical Centre of Groningen.

Appendix 2

Description of questionnaires

The International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form (ICIQ-UI-SF): This is a self-completed questionnaire that measures frequency, volume, and impact on daily life of involuntary urine loss. Scores range from 0 to 21, with higher scores correlating with worse incontinence. This questionnaire measures patient-reported outcomes in UI and is recommended by the International Consultation on Incontinence.

The Three Incontinence Questions (3IQ): This is a simple and quick questionnaire with acceptable accuracy for classifying urge and stress incontinence, appropriate for use in primary care. The questions correspond with the three questions recommended in the Dutch guideline on UI for assessing the type of incontinence (i.e., stress UI, urgency UI, and mixed UI).

Condition-specific quality of life (ICIQ-LUTS-QoL): a psychometrically robust patient-completed questionnaire evaluating quality of life in patients with UI, which is used in research and clinical practice worldwide. It has received a Grade A recommendation from the International Continence Society for use in women with UI. The overall score ranges from 19 to 76.

Generic Health-related Quality of Life (EQ-5D-5L): This is a commonly used measurement of general health status, with good validity and reliability reported in various health conditions. Health states, as defined by the five-dimensional descriptive system of this questionnaire, will be converted into a weighted health state index, using the EuroQol crosswalk value set. *Patient-reported Global Impression of Improvement (PGI-I):* This is a single item index, measured on a seven-point Likert scale (very much better, much better, a little better, no change, a little worse, much worse, very much worse)

P*elvic Organ Prolapse/Incontinence Sexual Questionnaire, International Urogynecological Association-revised (PISQ-IR)*: This is the only instrument validated in both sexually active and sexually inactive women with pelvic floor dysfunction.

The Institute of Medical Technology Assessment-Medical Consumption Questionnaire and iMTA Productivity Costs Questionnaire (iMTA-MCQ and iMTA-PCQ): The adjusted versions of these questionnaires are used to measure the use of healthcare and non-healthcare resources.

CHAPTER 3

Recruitment Through Media And General Practitioners Resulted In Comparable Samples In An RCT On Incontinence

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Werving deelnemers

URINCONTROL ONDERZOEK

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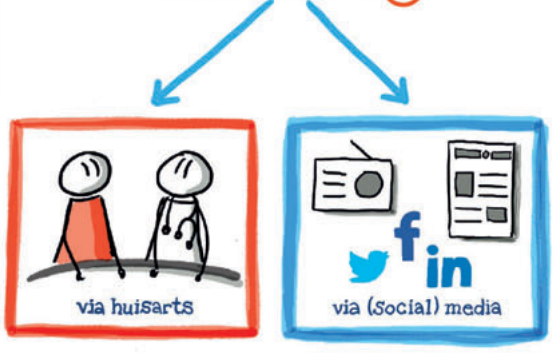

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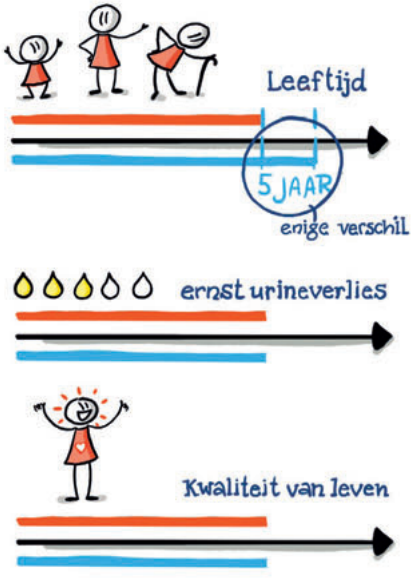


conclusie

(social)media is geschikt om deelnemers te werven voor onderzoek naar aandoeningen waar een taboe op rust

J. Clin. Epidemiolog. 2020

VISUALPOWER050

ABSTRACT

Objective: To assess the impact of recruitment strategy on the baseline characteristics of patients recruited in a randomized controlled trial for treating women with urinary incontinence.

Study Design and Setting: We conducted a cross-sectional analysis of baseline data from an earlier trial. Women were recruited through the media (including social media) or from participating general practices. Baseline characteristics were compared by univariate testing. Logistic regression analysis was performed to study the association between recruitment type and multiple baseline characteristics.

Results: The only differences between recruitment methods were in patient age, with those recruited through the media being significantly older than those recruited through general practice. The mean age difference was 5.0 years (95% confidence interval 2.2–7.9).

Conclusion: Samples recruited through the media and through case identification were largely comparable. Therefore, recruitment through the media may be a viable alternative to recruitment through primary care. This may be especially relevant for research on eHealth treatment for conditions with which patients experience barriers when seeking healthcare.

INTRODUCTION

Recruitment in clinical trials is often problematic, with reports indicating that only around 55% of clinical trials succeed in recruiting the prespecified target sample size,[1] and around 11% of all trials involving patients being discontinued because of poor recruitment.[2] This has also been observed in trials in primary care in the Netherlands, where it was shown that almost 40% of projects needed to be extended by at least 50% to obtain the target sample size.[3] When this problem arises, other recruitment strategies may be appropriate, such as recruiting patients via the media, including social media. Indeed, recruitment through (social) media has been found to be cost-effective in studies on mobile health interventions for healthy infant feeding practices,[4] the treatment of heavy-drinking smokers,[5] and weight loss in postmenopausal obese women.[6] However, unequal representation when using different recruitment strategies may lead to the possibility of different baseline characteristics.[7-9] This may have implications for studies on the effectiveness of an intervention and for the generalizability of study results.

We recently conducted a randomized controlled trial (RCT) to assess the non-inferiority of app-based treatment compared to usual care in women with urinary incontinence. In this trial, we had planned to recruit only incident and prevalent cases through general practitioners (GPs).[10] However, despite enough GPs agreeing to participate, we experienced problems because they often recruited no or very few patients. We therefore decided to expand recruitment to include the media, including social media, but we do not know if this sample is comparable to the women who were recruited by GPs. In this research, we aimed to analyze the impact of this change in recruitment strategy on the baseline characteristics of participants in the RCT.

METHODS

Study design and recruitment

The URinControl study was a mixed-methods study that used both quantitative and qualitative techniques to assess the impact of a mobile application for urinary incontinence in adult women. Part of the study involved a pragmatic non-inferiority RCT, for which an extensive description has been published elsewhere.[10] From July 2015 to November 2017 patients were recruited through GPs only, including both incident and prevalent (i.e., non-incident) cases. However, from November 2017 to June 2018, recruitment was done via both GPs and (social) media. All patients gave written informed consent before participating in the study.

Incident and prevalent cases were recruited through 89 participating GPs who agreed to recruit patients for the study. Prevalent cases were approached by letter in 14 of the 30 collaborating practices. The (social) media campaign consisted of the following: interviews in regional newspapers spread through LinkedIn, Facebook, and Twitter; interviews on national and regional radio, as well as local TV; and directed advertisements on Facebook in the study region.

Baseline characteristics

We collected characteristics during a baseline visit and through an online questionnaire. Medical and gynecological histories were obtained during these visits, and a research physician performed a physical examination to assess pelvic floor activity and prolapse. The online questionnaire assessed the impact of incontinence symptoms (using the ICIQ-UI-SF questionnaire),[11] quality of life (using the EQ-5D-5L, including the EQ-VAS),[12] disease-specific quality of life (using the ICIQ-LUTS-QoL),[13] and the impact of incontinence on sexual functioning (using the PISQ-IR).[14]

Analyses

Analyses were performed on complete cases with no imputation for missing data because the number of missing values was negligible at baseline. The characteristics of subjects in the two recruitment groups (i.e., GP-recruited and media-recruited cases) were compared by independent t-test or Mann-Whitney U tests for continuous data and by chi-square tests for categorical data, as appropriate.

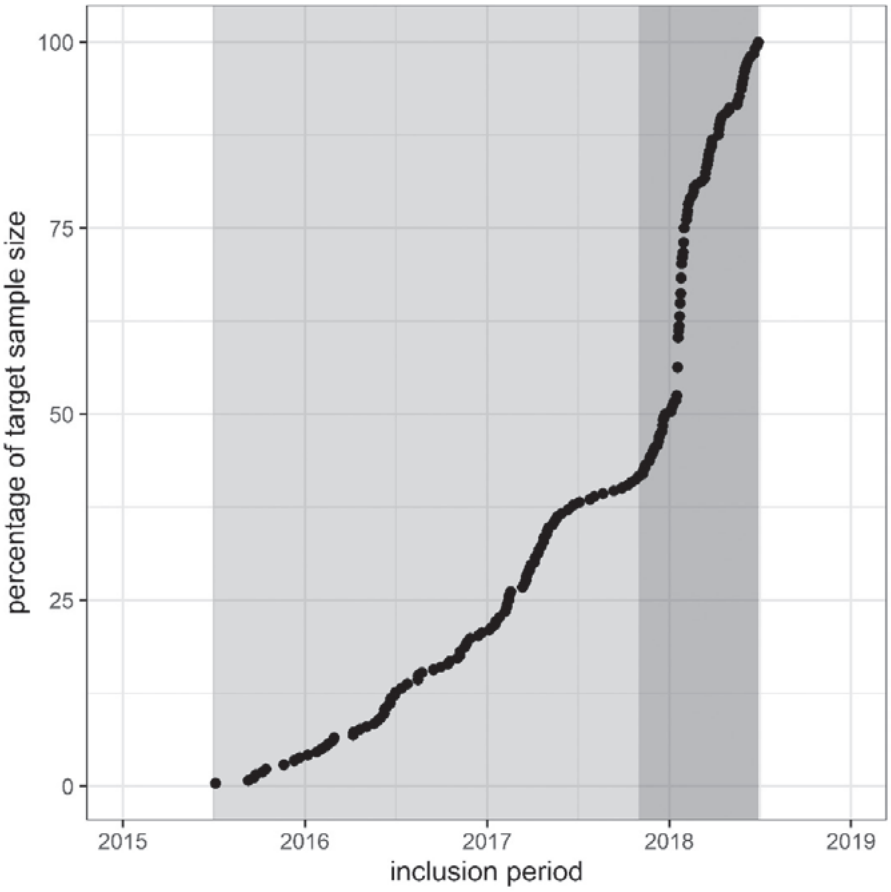
After the baseline assessments, we performed a simultaneous logistic regression analysis to study the association between recruitment type and multiple baseline characteristics. Seven putative variables were then selected: age, duration of complaints, ICIQ-UI score, type of urinary incontinence (stress or urgency), previous physical therapy for urinary incontinence (yes or no), history of pregnancy (yes or no), and postmenopausal. Multicollinearity between variables was assessed, model fit was assessed by the Hosmer–Lemeshow test and explained variance by the Nagelkerke R^2. All analyses were performed using IBM SPSS for windows, Version 25.0 (IBM Corp., Armonk, NY), using a two-sided alpha of 0.05. A Bonferroni correction was applied based on 29 tests resulting in an alpha of 0.002.

RESULTS

Trial recruitment

In total, 262 women were included and randomized, of whom 256 (98%) had complete baseline data and were included for analysis. Thereby the trial met its target sample size of 250 women.[10] Because of a higher than expected loss to follow-up 12 additional women were recruited. The recruitment trajectory of the trial is shown in Figure 1. Recruitment of participants through 89 GPs resulted in the inclusion of approximately 4 participants per month, recruitment through the media resulted in the inclusion of approximately 14 participants per month (Figure 1).

Figure H3.1. Recruitment trajectory of the trial over time. During the first part of the trial participants were recruited through GPs only (light gray area). During the last part of the trial participants were also recruited through the media (dark gray area.



Differences in baseline characteristics

Among the 108 participants recruited through (social) media, 48 indicated that they had heard about the study through traditional media, 38 through social media, and 22 provided no data on the source. Univariate comparisons among the groups showed a difference only for age (Table 1, t = -3.495, df = 254, p=0.001). The mean difference in age was 5.0 years (95% confidence interval 2.2-7.9).

Table 2 shows the results of the logistic regression analysis. Duration of symptoms was transformed because of a skewed distribution using a natural log transformation. Again age was the only factor that differed between recruitment types.

Table 1. Baseline characteristics. Univariate comparison of patient characteristics by recruitment methods

	GP recruited	Media recruited	p-value
	N = 148	N = 108	
Allocation: intervention/care as usual, N	75/73	54/54	
General characteristics			
Age (Mean ± SD)	50.1 ± 11.1	55.2 ± 11.8	0.001
BMI (Mean ± SD)	28.0 ± 5.4	27.2 ± 5.2	0.230
Gynecological history and status			
Postmenopausal status, N (%)			
Not postmenopausal	80 (54.1)	47 (43.5)	0.246
Postmenopausal	63 (42.6)	56 (51.9)	
Unknown due to anticonception	5 (3.4)	5 (4.6)	
Number of pregnancies, N (%)			
0	15 (10.1)	10 (9.3)	0.832
1	15 (10.1)	14 (13.0)	
2	54 (36.5)	42 (38.9)	
≥3	64 (43.2)	42 (38.9)	
Number of vaginal deliveries, N (%)			
0	25 (16.9)	17 (15.7)	0.882
1	21 (14.2)	15 (13.9)	
2	60 (40.5)	49 (45.4)	
≥3	42 (28.4)	27 (25.0)	
Hysterectomy, N (%)	14 (9.5)	9 (8.3)	0.756
Other abdominal surgery, N (%)	51 (34.5)	40 (37.0)	0.670
Patient reported feeling of prolapse, N (%)	13 (8.8)	5 (4.6)	0.199
Prolapse (POP-Q stadia), N (%)			
Stadium 0	23 (15.5)	18 (16.7)	0.197
Stadium 1	61 (41.2)	55 (50.9)	
Stadium 2A	64 (43.2)	35 (32.4)	
Pelvic floor functioning, N (%)			

	GP recruited	Media recruited	p-value
	N = 148	N = 108	
Normal	45 (30.4)	38 (35.2)	0.832
Overactive	23 (15.5)	17 (15.7)	
Underactive	79 (53.4)	53 (49.1)	
Inactive	1 (0.7)	0 (0.0)	
Incontinence complaints			
Duration of urinary incontinence (years; median | IQR)	7 | 8	9.5 | 15.25	0.077
Urinary incontinence type, N (%)			
Stress incontinence	61 (41.2)	46 (42.6)	0.458
Urgency incontinence	10 (6.8)	12 (11.1)	
Mixed (stress primary)	40 (27.0)	30 (27.8)	
Mixed (urgency primary)	37 (25.0)	20 (18.5)	
Impact of urinary incontinence symptoms (ICIQ-UI-SF sum score; mean ± SD)	9.6 ± 3.5	10.2 ± 3.0	0.165
Previous physical therapy for urinary incontinence	43 (29.1)	22 (20.4)	0.115
Quality of life			
General			
EQ-5D-5L, index score (median | IQR)	0.89 | 0.18	0.89 | 0.18	0.618
EQ-VAS (median | IQR)	80 | 25	80 | 22	0.844
Disease specific			
ICIQ-LUTS-QoL (median | IQR)	31 | 10	32 | 8.75	0.059
urinary incontinence and sexuality			
PISQ-IR			
Sexually active, N (%)	118 (79.7)	74 (68.5)	0.041
Not sexually active	N = 30	N = 34	
NSA-PR	50 | 50	50 | 50	0.650
NSA-CS	27.8 |66.7	16.7 | 55.6	0.504
NSA-GQ	28.6 | 50	32.1 | 35.7	0.951
NSA-CI	11.1| 36.1	5.6 | 44.4	0.983
Sexually active	N = 118	N = 74	
SA-PR	88.8 | 22.2	77.8 | 33.3	0.278
SA-CS	66.6 | 16.7	66.6 | 10.4	0.910
SA-GQ	40 | 26.7	47 | 28.3	0.166
SA-CI	75 | 8.3	75 | 16.7	0.987
SA-AO	56.3 | 18.8	56.3 | 13	0.481
SA-D	50 | 83.3	50 | 16.7	0.217

*statistically significant after Bonferroni correction (alpha after correction = 0.002)

Table 2. Results of logistic regression analysis testing the association between multiple baseline characteristics and type of recruitment.

	Odds ratio for media recruitment	
	OR (95% CI)	**P-value**
Age	1.06 (1.03-1.10)	0.001*
Postmenopausal status (ref = not menopausal)		
Postmenopausal	0.56 (0.24-1.33)	0.188
Unknown due to anticonception	1.10 (0.28-4.28)	0.895
Previous pregnancy (ref = no previous pregnancy)	0.77 (0.29-2.01)	0.589
Duration of symptoms (natural log transformation)	1.26 (0.95-1.67)	0.104
Type of incontinence (ref = stress incontinence)	0.76 (0.40-1.43)	0.397
ICIQ-UI-SF baseline score	1.06 (0.97-1.15)	0.207
Previous physical therapy (ref = no physical therapy)	0.51 (0.28-4.28)	0.037
Nagelkerke R^2 = 0.122 Hosmer and Lemeshowtest = 0.467		

*statistically significant after Bonferroni correction (alpha after correction = 0.002)

DISCUSSION

Summary of results

Different recruitment strategies can lead to differences in the characteristics of recruited samples. In our RCT of app-based treatment for urinary incontinence, however, samples recruited by two different strategies were largely comparable. Indeed, there was only a difference in age between cases recruited through GPs and cases recruited through (social) media, with the latter group being an average of 5.0 years older. Although this difference was clearly present, there was no impact on age-related outcomes, such as disease symptoms, menopausal status, or quality of life. When combining multiple baseline characteristics, age again was the only factor that differentiation between recruitment types.

Literature

In this study, recruitment through the media comprised both traditional media (e.g., newspaper items, radio, and TV) and social media (e.g., Facebook, LinkedIn, and Twitter). Although recruitment through the media was almost evenly distributed between traditional and social media, we were unable to compare the two. In a review that compared recruitment by social

media to that by other methods, only a few studies were reported to have compared the characteristics of patients recruited by traditional and social media.[15] Of note, it was reported that the relationship with age was contradictory between studies. Two studies of smoking cessation found that subjects recruited through social media were younger than those recruited with traditional methods, such as flyers, newspapers, and word of mouth.[9,16] By contrast, a study on lung cancer screening indicated that there were no age differences between subjects recruited through social media and through newspaper advertisements.[17] In some studies included in the review,[15] differences were found in ethnicity, education level, and socioeconomic status between methods, and it should be noted that these variables were not included in the present study. The authors concluded that recruitment via social media typically led to samples that were not comparable to those recruited by other methods.[15] Nevertheless, this judgment was made on the basis of a difference on a single variable. Another systematic review concluded that recruitment through Facebook led to a group of participants that was representative of traditional methods except for a few minor differences.[18] One difference was that participants were generally younger when recruited through Facebook.

To date, no reviews have identified studies that have directly compared participant characteristics after recruitment through a GP or social media.[15] Indeed, there is only sparse literature comparing recruitment by GPs with recruitment by traditional media. One study of childhood obesity used, among other methods, referral from health care professionals and traditional media for recruitment; but, results were only aggregated for active and passive recruitment methods.[19] Active recruitment (i.e., directly contacting a subject from a defined subject pool) was used in our recruitment of GP cases, whereas passive recruitment (i.e., a general invitation to participate) was used in our media recruitment.[20] The comparison between such active and passive methods of recruitment has been made in other studies. In those focusing on lifestyle interventions, for example, subjects recruited through passive methods had more favorable lifestyles, indicating a selection bias.[20,21] Such bias, indicating a tendency to attract subjects with certain health or disease statuses, was not apparent in the present study.[22]

Interpretation of outcomes

The average age difference of 5 years between our study groups was significant, and this finding is particularly relevant for incontinence, which is an age-related condition in which severity increases with age.[23] Therefore, including (social) media cases with a higher age may potentially have resulted in including women with more severe symptoms, yet this was not observed and disease symptoms were comparable between groups. A reason for the difference in age between (social) media cases and GP cases may be that older women do not seek help for their complaints because they assume that the symptoms reflect normal aging.[24] Thus, the older ages among women recruited through the media may reflect a successful public health campaign that accessed more women with erroneous beliefs.

Limitations

A limitation of this research is that it was not powered for the analyses performed, because the primary aim was to look at the effectiveness of app-based treatment compared to care-as-usual. Another limitation is that relevant comparison variables may not have been measured (e.g., socioeconomic status) because the study was not designed to compare recruitment methods.

Implications of changing recruitment strategy

In the base study for the present research, we would not have reached the target sample size within a reasonable time without using (social) media recruitment. Although the rationale for using (social) media for recruitment was to speed up the recruitment process, the increase in recruitment rate emphasizes that recruitment through (social) media has an important role for women with incontinence, which is a frequent problem for which many women do not seek care despite having significant symptom burdens.[24] Improved attention through (social) media may overcome the barriers to seeking health care for women who experience this problem. However, using such a recruitment strategy changes the target population from women that visit their GP for UI, to also include women that are not in GP records with UI complaints.

Conclusions

In conclusion, despite a difference in age, recruitment through the media rather than by case identification during consultations had no major impact on the sample that was finally recruited for our study. This will be of particular relevance to future studies given that only a small proportion of women with urinary incontinence seek care through routine consultations,[25,26] which potentially limits sample sizes or necessitates prohibitively long study periods. Recruitment through the media, including social media, could therefore serve as an alternative recruitment strategy to increase study engagement.

REFERENCES

1. Sully BG, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. Trials 2013;14:166,6215-14-16610.1186/1745-6215-14-166 [doi].
2. Kasenda B, von Elm E, You J, Blumle A, Tomonaga Y, Saccilotto R, et al. Prevalence, characteristics, and publication of discontinued randomized trials. JAMA 2014;311:1045-5110.1001/jama.2014.1361 [doi].
3. van der Wouden JC, Blankenstein AH, Huibers MJ, van der Windt DA, Stalman WA, Verhagen AP. Survey among 78 studies showed that Lasagna's law holds in Dutch primary care research. J Clin Epidemiol 2007;60:819-24S0895-4356(06)00434-3 [pii].
4. Laws RA, Litterbach EK, Denney-Wilson EA, Russell CG, Taki S, Ong KL, et al. A Comparison of Recruitment Methods for an mHealth Intervention Targeting Mothers: Lessons from the Growing Healthy Program. J Med Internet Res 2016;18:e24810.2196/jmir.5691 [doi].
5. Bold KW, Hanrahan TH, O'Malley SS, Fucito LM. Exploring the Utility of Web-Based Social Media Advertising to Recruit Adult Heavy-Drinking Smokers for Treatment. J Med Internet Res 2016;18:e10710.2196/jmir.5360 [doi].
6. Hsu MSH, Harper C, Gibson AA, Sweeting AN, McBride J, Markovic TP, et al. Recruitment Strategies for a Randomised Controlled Trial Comparing Fast Versus Slow Weight Loss in Postmenopausal Women with Obesity-The TEMPO Diet Trial. Healthcare (Basel) 2018;6:10.3390/healthcare6030076E76 [pii].
7. Adam LM, Manca DP, Bell RC. Can Facebook Be Used for Research? Experiences Using Facebook to Recruit Pregnant Women for a Randomized Controlled Trial. J Med Internet Res 2016;18:e250v18i9e250 [pii].
8. Stack JA, Paradis CF, Reynolds CF,3rd, Houck PR, Frank E, Anderson B, et al. Does recruitment method make a difference? Effects on protocol retention and treatment outcome in elderly depressed patients. Psychiatry Res 1995;56:17-2401651781940 2617R [pii].
9. Frandsen M, Thow M, Ferguson SG. The Effectiveness Of Social Media (Facebook) Compared With More Traditional Advertising Methods for Recruiting Eligible Participants To Health Research Studies: A Randomized, Controlled Clinical Trial. JMIR Res Protoc 2016;5:e16110.2196/resprot.5747 [doi].
10. Loohuis AMM, Wessels NJ, Jellema P, Vermeulen KM, Slieker-Ten Hove MC, van Gemert-Pijnen JEWC, et al. The impact of a mobile application-based treatment for urinary incontinence in adult women: Design of a mixed-methods randomized controlled trial in a primary care setting. Neurourol Urodyn 2018;37:2167-7610.1002/nau.23507 [doi].
11. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn 2004;23:322-3010.1002/nau.20041 [doi].
12. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727-3610.1007/s11136-011-9903-x [doi].
13. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. Br J Obstet Gynaecol 1997;104:1374-9.
14. Rogers RG, Rockwood TH, Constantine ML, Thakar R, Kammerer-Doak DN, Pauls RN, et al. A new measure of sexual function in women with pelvic floor disorders (PFD): the Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR). Int Urogynecol J 2013;24:1091-10310.1007/s00192-012-2020-8 [doi].
15. Topolovec-Vranic J, Natarajan K. The Use of Social Media in Recruitment for Medical Research Studies: A Scoping Review. J Med Internet Res 2016;18:e286v18i11e286 [pii].

16. Frandsen M, Walters J, Ferguson SG. Exploring the viability of using online social media advertising as a recruitment method for smoking cessation clinical trials. Nicotine Tob Res 2014;16:247-5110.1093/ntr/ntt157 [doi].

17. Carter-Harris L, Bartlett Ellis R, Warrick A, Rawl S. Beyond Traditional Newspaper Advertisement: Leveraging Facebook-Targeted Advertisement to Recruit Long-Term Smokers for Research. J Med Internet Res 2016;18:e11710.2196/jmir.5502 [doi].

18. Whitaker C, Stevelink S, Fear N. The Use of Facebook in Recruiting Participants for Health Research Purposes: A Systematic Review. J Med Internet Res 2017;19:e29010.2196/jmir.7071 [doi].

19. Fleming J, Kamal A, Harrison E, Hamborg T, Stewart-Brown S, Thorogood M, et al. Evaluation of recruitment methods for a trial targeting childhood obesity: Families for Health randomised controlled trial. Trials 2015;16:535,015-1062-x10.1186/s13063-015-1062-x [doi].

20. Sarkin JA, Marshall SJ, Larson KA, Calfas KJ, Sallis JF. A comparison of methods of recruitment to a health promotion program for university seniors. Prev Med 1998;27:562-71S0091-7435(98)90327-9 [pii].

21. Manjer J, Elmstahl S, Janzon L, Berglund G. Invitation to a population-based cohort study: differences between subjects recruited using various strategies. Scand J Public Health 2002;30:103-1210.1080/14034940210133771 [doi].

22. Warren FC, Stych K, Thorogood M, Sharp DJ, Murphy M, Turner KM, et al. Evaluation of different recruitment and randomisation methods in a trial of general practitioner-led interventions to increase physical activity: a randomised controlled feasibility study with factorial design. Trials 2014;15:134,6215-15-13410.1186/1745-6215-15-134 [doi].

23. Melville JL, Katon W, Delaney K, Newton K. Urinary incontinence in US women: a population-based study. Arch Intern Med 2005;165:537-42165/5/537 [pii].

24. Visser E, de Bock GH, Kollen BJ, Meijerink M, Berger MY, Dekker JH. Systematic screening for urinary incontinence in older women: who could benefit from it?. Scand J Prim Health Care 2012;30:21-810.3109/02813432.2011.628244 [doi].

25. Schreiber Pedersen L, Lose G, Hoybye MT, Jurgensen M, Waldmann A, Rudnicki M. Predictors and reasons for help-seeking behavior among women with urinary incontinence. Int Urogynecol J 2018;29:521-3010.1007/s00192-017-3434-0 [doi].

26. O'Donnell M, Lose G, Sykes D, Voss S, Hunskaar S. Help-seeking behaviour and associated factors among women with urinary incontinence in France, Germany, Spain and the United Kingdom. Eur Urol 2005;47:385,92; discussion 392S0302-2838(04)00502-0 [pii].

CHAPTER 4

App-Based Treatment For Urinary Incontinence Non-Inferior To Care As Usual In Primary Care. Results Of A Pragmatic, Randomized Controlled Trial

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App versus standaard zorg

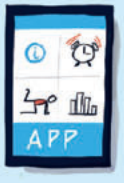
URINCONTROL ONDERZOEK

Impact

1 op de 3 vrouwen

Onderzoek

Resultaten



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ABSTRACT

Purpose: App-based treatment is promising for common diseases with good conservative management options, like urinary incontinence (UI) in woman, but the effectiveness is unclear compared to care-as-usual. This study set out to determine if app-based treatment for women with stress, urgency, or mixed UI was non-inferior to care-as-usual in primary care.

Methods: A pragmatic, randomized controlled, non-inferiority trial in Dutch primary care including adult woman with ≥2 episodes of UI per week. From 2015 to July 2018 350 women were screened for eligibility. A stand-alone app-based treatment with pelvic floor muscle and bladder training was compared to care-as-usual according to the Dutch GP guideline for UI treatment. Effects measured were change in symptom severity score from baseline to 4 months (primary outcome), impact on disease-specific quality of life, patient perceived improvement and number of UI episodes. Non-inferiority (<1.5 points) was analyzed on by linear regression.

Results: The 262 eligible women were randomized equally; 195 patients attended follow-up. The change in symptom severity with app-based treatment (-2.16; 95%CI, -2.67 to -1.65) was non-inferior compared to care-as-usual (-2.56; 95%CI, -3.28 to -1.84), with a mean difference of 0.058 points (95% CI -0.776 to 0.891) between groups. Neither treatment was superior to the other, and both groups showed improvements in outcome measures after treatment.

Conclusion: App-based treatment for women with UI was at least as effective as care-as-usual in primary care. As such app-based treatments may provide women with a good alternative for consultation.

INTRODUCTION

Conservative treatment for female urinary incontinence (UI) can be time-consuming and adherence varies, which limit its effectiveness.[1] App-based treatment that delivers advice, training, and motivation for managing UI in isolation could offer advantages over care-as-usual , removing the barriers to treatment access and improving adherence to training. However, we cannot justify prescribing an app for UI if it cannot at least be shown to be non-inferior to current best practice.

There already exist over 100 apps for UI management, yet evidence for their effectiveness is scarce. Moreover, these apps tend to focus on stress UI alone and to have diverse contents.[2] In a Swedish study, app treatment improved UI symptoms and quality of life after 3 months compared to postponed treatment and was cost-effective at 12 months.[3] A recent small Brazilian study also showed increased adherence to pelvic floor muscle exercises and an improvement in UI symptoms after 3 months of app-based treatment compared with written instructions alone.[4] To date, there have been no studies comparing app-based treatment to care-as-usual, or treatment for urgency or mixed UI. This is important because the majority of women with UI have stress, urgency or mixed-type UI.[5]

We developed an App for use by women with stress, urgency, and mixed UI, requiring no caregiver support. In this study, we specifically assessed whether app-based treatment with this tool was non-inferior to care-as-usual provided by general practitioners (GPs) after 4 months.

METHODS

We conducted a pragmatic, parallel arm, non-inferiority trial of patients with stress, urgency, or mixed UI. The complete study protocol was published previously. [6] After trial commencement, an amendment to the protocol added a process evaluation method and changes to recruit participants from the general population because of a low inclusion rate.[7] We followed the CONSORT guideline and the relevant extensions.[8, 9]

We recruited participants via primary care, the lay press, and social media in the north of the Netherlands from July 2015 through July 2018. In primary care, women who consulted for UI were invited during consultation. Women who had previously consulted for UI received postal invitations. Participants recruited through the lay press and social media could sign up directly via a dedicated website to receive information on the study. We confirmed the diagnosis of UI by the Three Incontinence Questions (3IQ) questionnaire.[10]

Adult women with ≥2 episodes of UI per week, access to a smartphone or tablet, and a wish to be treated were eligible. We excluded woman with conditions or therapy that could

complicate UI, those who had undergone treatment for UI in the previous year (including surgery), those unable to complete the questionnaire in Dutch, and those with terminal illness or current severe mental illness (e.g. dementia). Appendix E1 presents the full inclusion and exclusion criteria.

Interventions

App-based treatment group

Our app, named URinControl, contained a step-by-step program for the self-management of UI that was based on relevant Dutch GP and international guidance for treating UI.[11, 12] We reported details on the development and content of this app previously.[6]

Participants received a personal account and instructions to download and install the app on their smartphone or tablet. The research team provided technical support only. Each participant was free to contact her GP with any questions regarding UI and to receive additional treatment. The only harm of this treatment that we anticipated was the possibility of performing the exercises in an incorrect matter resulting in a symptom increase. Therefore, the app recommends patients to visit a doctor if the treatment does not lead to improvement after 3 months, or if the patient develops other health issues.

Care-as-usual group

Participants in the care-as-usual group were referred to their own GP to discuss treatment options. GPs were advised to follow the relevant Dutch GP guideline,[11] without limitations on the type and mode of treatment. Care-as-usual could consist of any of the following, alone or in combination: instructions on pelvic floor muscle training (PFMT) and/or bladder training; prescribing a pessary, drugs, or absorbent products; referral to a continence nurse, a pelvic physical therapist, or secondary care. [11] GPs received no explanation about the content of the app and the participants received no additional information on UI from the researchers. No harms of treatment were anticipated in the study protocol.

Outcomes

Participants completed the study questionnaires and a 3-day frequency volume (FV) chart of voiding before attending the baseline assessment. At the appointment, they provided information on parity, related medical history, comorbidity, and drug use. A trained research physician measured weight and height and performed a urogynecological assessment. The physician graded prolapse stage according to the Pelvic Organ Prolapse Quantification System and rated pelvic floor muscle function according to ICS guidance.[13] We repeated the web-based questionnaires and FV-chart after 4 months. Our published protocol describes the assessment of outcome measures in further detail.[6]

The primary outcome was the difference between groups in the change of UI severity from baseline to 4 months, assessed by the International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form (ICIQ-UI-SF). [14, 15] Secondary outcomes were the differences between groups in the change in the condition-specific quality of life (ICIQ-LUTS-QoL) and the change in the of number of UI episodes per day from baseline to 4 months (assessed with FV chart), and the patient global impression of improvement of incontinence (PGI-I) at 4 months.[16]

Randomization and blinding

The researcher confirmed eligibility, gained signed informed consent, collected baseline data and enrolled the participant in the study. Participants were then randomized by 1:1 allocation with random block sizes stratified at the GP level. This was performed using ALEA, a computer program, to ensure full concealment of group allocation.[17] It was not possible to blind participants or care providers, or data collection to treatment allocation. The data analysts were blinded at the time of data cleaning and analyses.

Sample size

The study has a non-inferiority design which uses a non-inferiority margin to reject or accept non-inferiority. The margin for non-inferiority was set to a 1.5-point difference in the change score for UI severity between groups, based on the requirement for a minimally important difference in the ICIQ-UI-SF of 1.58 points.[18] Sample size calculation was based on an estimated correlation coefficient of 0.4 between baseline and follow-up scores of the ICIQ, power of 0.80, one-sided type I error of 0.025 and an estimated non-inferiority margin of 1.5 points and a standard deviation of 4.1. We needed a sample of 100 participants per group. Allowing for an expected loss-to-follow-up of up to 20%, we aimed to enroll 250 participants. Although we enrolled women with all types of UI, the study was underpowered to show difference in outcome according to UI type.

Statistical methods

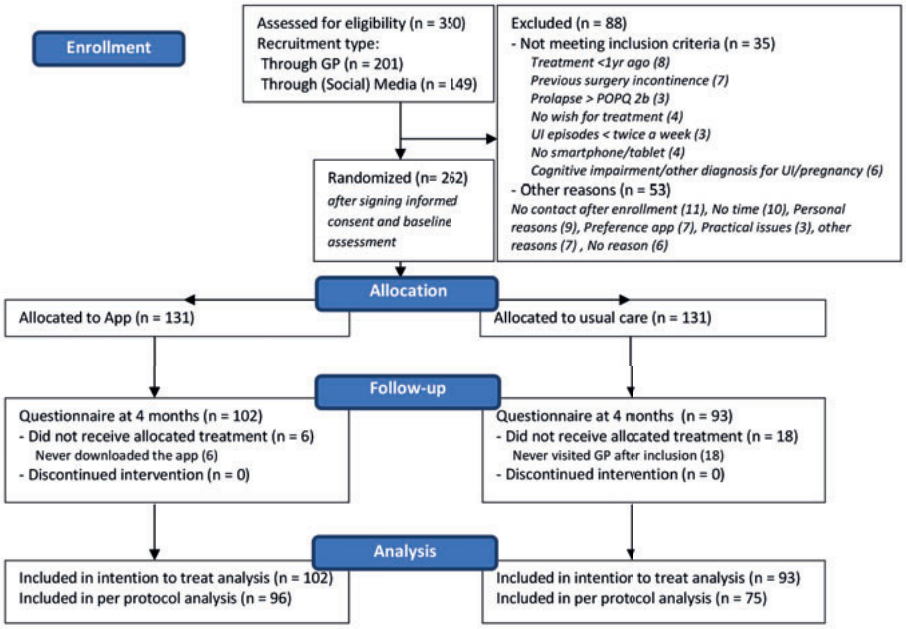
The primary outcome was analyzed using linear regression. We accepted non-inferiority of the app-based treatment group to the care-as-usual group if the upper limit of the 95% confidence interval (CI) of the difference in change was less than the non-inferiority margin of 1.5 points. If the upper limit of the 95% CI was also less than zero, we concluded that there was statistically significance evidence of the superiority of app-based treatment (2-sided p-value <0.05). We performed both intention to treat (ITT) and per protocol (PP) analyses to give conservative outcomes suitable for a non-inferiority design.[19, 20] PP analyses will be presented in full in the appendices. We assessed superiority on an ITT basis for the secondary outcomes, using linear regression analysis for the LUTS-QoL and the Mann–Whitney *U* test for the PGI-I and number of UI episodes. Results were considered statistically significant for p-values of <0.05.

The regression analyses included baseline UI severity score as a covariate. We also performed analyses in the following pre-specified subgroups: incontinence type (stress, urgency, or mixed UI), previous physical therapy for UI (yes/no), and recruitment strategy (through GP or media). We used IBM SPSS for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA) for all analyses.

RESULTS

Participants entered the study through 88 GPs from 31 practices (n = 201), or social and other media (n = 149). Of the 350 screened participants, 262 were eligible and randomized equally (Figure 1). We extended the study to include more participants because loss to follow-up was 6% higher than expected. Follow-up ended on 20th December 2018.

Figure H4.1. Flow diagram of participants URinControl-trail



The mean age of the participants was 53 years (range 20–86 years) and the median duration of UI was 7 years (Interquartile range 4–14 years). Fifty percent (n=130) reported having mixed UI, and the overall severity of UI was rated as slight by 10% (n = 26), moderate by 64% (n = 166), and severe by 26% (n = 67). Despite randomization, women in the care-as-usual group tended to have more severe UI and a higher frequency of stress UI (Table 1).

Table 1. Baseline characteristics of participants assigned to App-based treatment or usual care

Characteristics	App-treatment	N*	Care as usual	N*
Age, (years)	53.2 ± 12.8	131	51.3 ± 10.3	131
Body mass index (kg/m²)	27.6 ± 5.5	130	28.0 ± 5.2	131
Higher educational level	53 (52.0%)	102	48 (51.6%)	93
≥1 Vaginal births	111 (85.4%)	130	105 (80.2%)	131
Postmenopausal status, yes	64 (49.2%)	130	59 (45.0%)	131
Recruitment type		131		131
General practitioner	76 (58.0%)		76 (58.0%)	
Lay press or social media	55 (42.0%)		55 (42.0%)	
Duration of UI (years)	7 (4–14)	130	8 (4–13)	131
Type of UI		131		131
Stress	50 (38.2%)		60 (45.8%)	
Mixed, stress predominant	37 (28.2%)		33 (25.2%)	
Urgency	12 (9.2%)		10 (7.6%)	
Mixed, urgency predominant	32 (24.4%)		28 (21.4%)	
Previous treatment for UI		130		131
None	99 (76.2%)		95 (72.5%)	
Pessary			1 (0.8%)	
Physical therapist	31 (23.8%)		35 (26.7%)	
Incontinence severity				
ICIQ-UI SF score	9.5 ± 3.2	130	10.3 ± 3.4	129
ICIQ-LUTSqol score	33.9 ± 8.3	130	33.4 ± 7.8	129
UI (per day)	1.0 (0.33–2.33)	130	1.0 (0.33–2.33)	129

Values are means ± standard deviation, numbers (%), or medians (interquartile range). *Explanation differences in N: missing data of one baseline assessment and three baseline questionnaires. Educational level was assessed at follow-up. Abbreviations: ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; ICIQ-LUTSqol, ICIQ lower urinary tract symptoms quality of life; UI, urinary incontinence.

At 4 months, 102 women in the app-based treatment group (78%) and 93 women in the care-as-usual group (71%) were available for the ITT analysis. Loss to follow-up was associated with young age, higher body mass index, and no prior treatment (data shown in appendix table E2). In the app-based treatment group, 96 (94%) used the app at least once, 6 (6%) underwent PFMT, and 4 (4%) received additional medication. In the care-as-usual group, 75 (81%) visited their GP, of whom 38 (41%) were referred to a therapist or specialist nurse for PFMT and 5 (5%) received medication. No participants were referred to a specialist. Thus, 96 women in the app-based treatment group and 75 women in the care-as-usual group were eligible for the per protocol analysis. Baseline characteristics of the per protocol study sample are shown in appendix table E3.

The ITT mean difference in change scores for UI severity between the app-based treatment and care-as-usual groups was 0.06 points (95% CI: -0.776 to 0.891). The upper limit of the 95% CI did not reach the non-inferiority margin, but it did cross the null hypothesis line of zero (Table 2, Figure 2). Thus, app-based treatment was non-inferior but non-superior to care-as-usual. Both groups showed improvements after treatment, with mean changes in UI severity of -2.16 points (-2.67 to -1.65) in the app-based treatment group and -2.56 points (-3.28 to -1.84) in the care-as-usual group. The analysis of the unadjusted scores for change from baseline and the analysis in the PP study sample produced comparable results are shown in appendix table E4 and E5. There was no evidence that the intervention effect differed by UI type, prior physical therapy for UI, or recruitment strategy (Table 3).

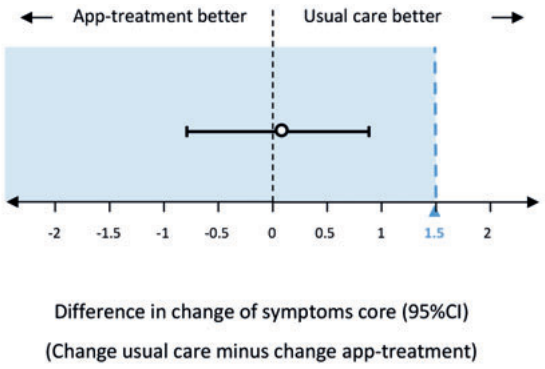
Neither treatment option was superior to the other. In both groups, the disease-specific quality of life (LUTS-QoL) improved and the number of UI episodes women experienced per day decreased. Also, most women in the app-based treatment (65.7%) and care-as-usual (66.6%) groups had improved PGI-I results (Table 2).

Table 2. Change of mean (SD) questionnaire scores from baseline to follow-up by group allocation and adjusted difference (95% CI) between groups

	Change from baseline				Adjusted difference (95% CI) or p-value
Outcomes	**App-treatment**	**N**	**Care as usual**	**N**	
ICIQ-UI SF score	-2.16 ± 2.56	101*	-2.56 ± 3.51	93	0.058 (-0.776 to 0.891)
ICIQ-LUTS-qol score	-4.34 ± 5.44	101*	-3.78 ± 5.90	93	-0.566 (-2.035 to 0.902)
PGI-I		102		93	P = 0.349 U-statistic
Very much better	2 (2.0%)		11 (11.8%)		
Much better	25 (24.5%)		20 (21.5%)		
A little better	40 (39.2%)		31 (33.3%)		
No change	30 (29.4%)		26 (28.0%)		
A little worse	3 (2.9%)		2 (2.2%)		
Much worse	2 (2.0%)		3 (3.2%)		
Very much worse	-		-		
UI (per day)	-0.61 ± 2.02	83	-0.48 ± 1.20	74	P = 0.705 U-statistic

Analyses performed on an intention to treat base. ICIQ-UI SF score and LUTS-qol score are adjusted for baseline. PGI-I and UI (per day) are unadjusted scores. Values are presented as means ± standard deviation or as numbers (%). Abbreviations: ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; ICIQ-LUTS-qol, ICIQ lower urinary tract symptoms quality of life; PGI-I, Patient global impression of improvement; UI, urinary incontinence. *One baseline-questionnaire missing.

Figure H4.2. Difference in change of ICIQ-UI-SF symptom score, 95% confidence intervals and non-inferiority margin.



Difference of change comparing change of UI-symptom score between usual care and App-based treatment. Blue dashed line at difference of change = 1.5 indicates non-inferiority margin. Blue tinted region to the left of margin indicates values for which App-treatment would be considered non-inferior to usual care. Black dashed line represents H0 hypothesis. Analysis performed on an intention to treat base adjusted for baseline scores. The per protocol analysis is shown in appendix table E5.

Table 3: Linear regression analysis of treatment effect within sub-groups, testing superiority of difference in change of ICIQ-UI SF score at 4 months

Subgroup	N	Treatment effect [95%CI]
Recruitment type		
General practitioner	107	-0.592 (-1.74 to 0.557)
Lay press or social media	87	0.598 (-0.634 to 1.831)
Type of UI		
Stress	76	-0.154 (-1.337 to 1.029)
Mixed, stress predominant	56	-0.230 (-1.780 to 1.740)
Mixed, urgency predominant	42	-0.345 (-1.972 to 1.281)
Urgency	20	0.401 (-3.910 to 4.710)
Previous physical therapy for UI		
No	137	-1.46 (-1.081 to 0.789)
Yes	57	0.149 (-1.701 to 1.999)
Primary analysis	262	

Analyses performed on an intention to treat base. UI, urinary incontinence; ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form.

DISCUSSION

Among women with stress, urgency, and mixed UI, therapy using the stand-alone URinControl app was at least as effective after 4 months as guideline-based care provided by GPs. Both treatments resulted in clinically relevant decrease of UI severity, improved quality of life, and fewer leakage episodes per day.

The main strength of this study is comparing app-based treatment with recommended care-as-usual.[5, 11] Other strengths lie in the method of app development and the use of a representative study population, comprising women most likely to benefit from app-based treatment. The proportion of women with mixed type UI was higher than expected, which might reflect selection bias. Also, patients lost to follow up were mostly younger without previous treatment, which might reflect a group with lower adherence to treatment. The inclusion criterion "the availability of a mobile phone or tablet" and the recruitment strategy using social media could have led to a selection of woman with already higher accessibility to healthcare and especially eHealth.

We adopted a pragmatic design because our interest lay in the effectiveness rather than the efficacy of the URinControl app in routine practice. We applied no strict treatment protocol in either group. In the care-as-usual group, this may have introduced a delay in attending

the GP or in a decision not to choose pelvic physiotherapy. These issues could have reduced the effectiveness of each treatment approach. We could not blind the participants or caregivers, which could have increased the motivation of participants to follow the new treatment or could have led to disappointment if they received care-as-usual. By contrast, not blinding the GP may have led to stricter guideline adherence.

Recruitment was an important challenge in this study, with a notably lower prevalence of UI in the participating practices than expected based on the known occurrence in Dutch primary care.[1, 11] We therefore changed our recruitment strategy during the study, seeking additional participants through (social) media.[7] Subgroup analyses indicated that recruitment did not introduce significant or clinically relevant differences in outcomes, but we cannot be certain that the data reflect all women who seek help for UI from their GPs. We reached 195 of the aimed 200 inclusions with complete follow-up. Therefore our study may be underpowered, especially for the subgroup analyses.

Two trials previously evaluated the effects of app-based treatment on stress UI. Asklund et al. demonstrated a greater improvement in symptom severity and condition-specific quality of life after app treatment for 3 months (n = 62) compared with postponed treatment (n = 61).[3] Their app included information on stress UI, a PFMT program, and the number and level of exercises performed, as well as a reminder system. Araujo et al. also studied the superiority of adherence to PFMT after 3 months based on app guidance (n = 17) compared to that based on written instructions (n = 16),[4] but showed no significant differences between the groups in either symptom severity or quality of life. Their app included PFMT with electromyography images, reminders, and an overview of their training and UI history.

In our study we combined PFMT for stress UI with bladder training for urgency and mixed UI, where others have focused on stress UI alone.[3, 4] Their choice was possibly motivated by experience with an internet-based program for stress UI or by the lack of literature on non-face-to-face treatment for urgency and mixed UI.[21] However, such an approach excludes the majority of women with symptomatic UI.

Symptom score reductions were slightly smaller in our study, compared to earlier publications.[3, 4] This could be due to the lower baseline UI severity scores, the inclusion of other types of UI, and the range of options available for care-as-usual in our study. Also, where our participants relied on self-motivation or the reminder function within the app, participants in the other studies received a reminder email from the researchers after 4 weeks, or a monthly check by a physical therapist.[3, 4] Adherence to treatment is an important topic in the treatment of UI but also in the continuation of eHealth-interventions. For this study, we chose a pragmatic approach for both care-as-usual and the app-based treatment, focusing on change of effect on UI severity without measuring adherence. However, with eHealth, self-registration within an app and automatically logged data (logdata) offer new ways to track adherence to treatment.

The effect sizes on UI severity were larger than a placebo effect, previously reported at 1.7 points, [22] and clinically relevant, with minimally important differences of 3.7 and 2.5 points tending to be reached for the LUTS-QoL and the ICIQ-UI SF, respectively.[18] There was an outlier for the ICIQ-UI SF in the app-based treatment group, but we considered all values to be clinically relevant because the scores for the treatment effect in the app-based treatment group were non-inferior or comparable to those in the care-as-usual group (i.e., above 2.5) and were higher than for placebo. [22]

The non-inferiority of app-based treatment will only be truly clinically relevant if we can demonstrate that it produces a better patient experience or that it is less expensive than care-as-usual, or has significant long-term outcomes. A patient might prefer the accessibility and ease of treatment in her own home or may benefit from some of the integrated functions of the app. The society may benefit from an effective treatment with lower costs. Our findings indicate that a GP can offer care-as-usual or app-based treatment to women seeking help for UI thanks to the comparable symptom improvement seen with each approach. We included treatment advices for all three main types of UI in our App, thereby increasing its applicability and relevance. However, there is a need to consider that women recruited through (social) media might have experienced barriers to seeking help directly from their GP, including shame, not knowing there are effective treatments, or simply thinking that their symptoms are a normal part of life.[1] Therefore, we recommend that GPs be more proactive in offering treatment advice and signposting for UI to woman in their practice. An app could be an effective way to remedy these unmet needs. In the meantime, we advocate that policy makers support critical websites like the NHS app library so that we may be better placed to translate the available data into guidance for patients and GPs.[23]

App-based treatment for female stress, urgency and mixed UI was at least as effective as, but not superior to care-as-usual. Although eHealth is clearly a promising and evolving route to healthcare access, researchers and clinicians have a responsibility to ensure that patients receive the best treatments that are currently available. We emphasize the importance of further research and of employing appropriate study designs to assess the effects of new apps in a more critical light.[24] In doing so, we may find that the purported positive effects of many apps are smaller in clinical settings. Future research should clarify both the long-term outcomes, and the barriers and facilitators to the use and implementation of app-based treatment.

REFERENCES

1. Visser E, De Bock GH, Kollen BJ, et al. Systematic screening for urinary incontinence in older women: Who could benefit from it? *Scand J Prim Heal Care.* 2012;30:21–8.
2. Loohuis A, Chavannes N. Medical apps; Care for the future? [Dutch]. *Huisarts Wet.* 2017;60:440–3.
3. Asklund I, Nyström E, Sjöström M, et al. Mobile app for treatment of stress urinary incontinence: A randomized controlled trial. *Neurourol Urodyn.* 2017;36(5):1369–76.
4. Araujo CC, Marques ADA, Juliato CRT. The Adherence of Home Pelvic Floor Muscles Training Using a Mobile Device Application for Women With Urinary Incontinence: A Randomized Controlled Trial. *Female Pelvic Med Reconstr Surg* [Internet]. 2019 [cited 2019 Feb 1];00:00–00. Available from: www.fpmrs.net
5. Abrams P, Andersson K-E, Apostolidis A, et al. 6th International Consultation on Incontinence. Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence. *Neurourol Urodyn* [Internet]. 2018 Sep [cited 2019 Apr 25];37(7):2271–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30106223
6. Loohuis AM, Wessels NJ, Jellema P, et al. The impact of a mobile application-based treatment for urinary incontinence in adult women: Design of a mixed-methods randomized controlled trial in a primary care setting. *Neurourol Urodyn.* 2018;37:2167–76.
7. Van der Worp H, Loohuis AMM, Flohil IL, et al. Recruitment through media and general practitioners resulted in comparable samples in an RCT on incontinence. *J. Clin. Epicemiol.* In press.
8. Zwarenstein M, Treweek S, Gagier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ.* 2008;337:a2390
9. Piaggio G, Elbourne DR, Pocock SJ et al. For the CONSORT Group. Reporting of noninferiority and equivalence randomized trials. Extension of the CONSORT 2010 statement. *JAMA.* 2012; 308(24): 2594-2604
10. Brown JS, Bradley CS, Subak LL, et al. The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. *Ann Intern Med.* 2006;144:715–23.
11. Damen-van Beek Z, Wiersma T. Practice guideline 'Urinary incontinence in women' from the Dutch College of General Practitioners. *Ned Tijdschr Geneeskd.* 2016;160:D674.
12. Dumoulin C, Hunter KF, Moore K, et al. Conservative management for female urinary incontinence and pelvic organ prolapse review 2013: Summary of the 5th International Consultation on Incontinence. *Neurourol Urodyn*. 2016;35:15–20.
13. Bump R, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obs Gynecol.* 1996;175(1):10–17.
14. Avery K, Donovan J, Peters TJ, et al. ICIQ: A brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn* [Internet]. 2004 [cited 2019 Jan 17];23(4):322–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15227649
15. Klovning A, Avery K, Sandvik H, et al. Comparison of two questionnaires for assessing the severity of urinary incontinence: The ICIQ-UI SF versus the Incontinence severity index. *Neurourol Urodyn.* 2009;(28):411–5.
16. Yalcin I, Bump R. Validation of two global impression questionnaires for incontinence. *Am J Obstet Gynecol.* 2003;189:98-101.
17. ALEA software for randomization in clinical trials. http://tenalea.net/Documents/ALEA/ALEARandomisationProgramFeatures.pdf.
18. Nyström E, Sjöström M, Stenlund H, et al. ICIQ symptom and quality of life instruments measure clinically relevant improvements in women with stress urinary incontinence. *Neurourol Urodyn.* 2015;

19. European Medicines Agency. ICH Topic E9 Regulations on statistics: Statistical principals for clinical trials (CPMP/ICH/363/96); [Internet]. 1998. Available from: http://www.emea.eu.int

20. Soonawala D, Dekkers OM. Non-inferiority studies: mogelijkheden en kanttekeningen. *Ned Tijdschr Geneeskd*. 2012;156(A4665):1–5.

21. Sjostrom M, Umefjord G, Stenlund H, et al. Internet-based treatment of stress urinary incontinence: A randomised controlled study. *Neurourol Urodyn*. 2012;31(6):706–1102.

22. Hampel C, Yalcin I, Voss S, et al. Effect of dose escalation on the tolerability and efficacy of duloxetine in the treatment of women with stress urinary incontinence. *Int Urogynecol J* [Internet]. 2006 [cited 2019 Feb 19];18(8):919–29. Available from: https://link.springer.com/content/pdf/10.1007%2Fs00192-006-0256-x.pdf

23. NHS Apps Library - NHS [Internet]. NHS Apps Library. [cited 2019 Feb 27]. Available from: https://www.nhs.uk/apps-library/

24. Byambasuren O, Sanders S, Beller E, et al. Prescribable mHealth apps identified from an overview of systematic reviews. *npj Digit Med*. 2018;12.

APPENDICES

Appendix E1: Full inclusion and exclusion criteria

We used the following inclusion criteria: female sex; age ≥18 years; self-reported stress, urgency, or mixed UI at least twice a week according to the Three Incontinence Questions (3IQ); wanting treatment; and access to a smartphone or tablet. Women are excluded in case of: indwelling urinary catheter, urogenital malignancy, previous surgery for UI, treatment for UI in the previous year (pharmacological or non-pharmacological), terminal or serious illness, cognitive impairment, psychiatric illness, urinary tract infection (UTI) (dipstick, and if negative, dipslide or urine culture), overflow or continuous UI, pregnancy or recent childbirth (<6 months ago) or the inability to complete a questionnaire in Dutch.

Appendix table E2: Loss to follow-up sample; baseline characteristics and analysis of differences with sample available for follow-up

Characteristics	Available at FU	N*	Loss to FU	N*	Difference (95%CI) or p-value
Age, (years)	53.4 ± 11.3	195	49.0 ± 12.2	67	**-4.445 (-7.654 to -1.237)**
Body mass index (kg/m²)	27.3 ± 5.0	195	29.3 ± 6.0	66	**1.997 (0.518 to 0.3475)**
Higher educational level	101 (51.8%)	195	No data at FU	-	-
≥1 Vaginal births	165 (84.6%)	195	51 (77.3%)	66	0.241 (X^2)
Postmenopausal status, yes	26 (39.4%)	195	26 (39.4%)	66	0.345 (X^2)
Recruitment type		195		67	0.154 (X^2)
General practitioner	108 (55.4%)		44 (65.7%)		
Lay press or social media	87 (44.6%)		23 (34.3%)		
Duration of UI (years)	8.0 (5–14)	195	5.2 (3–12)	67	0.062 (U-statistic)
Type of UI		195		67	0.104 (X^2)
Stress	76 (39.0%)		34 (50.7%)		
Mixed, stress predominant	56 (28.7%)		14 (20.6%)		
Urgency	20 (10.3%)		2 (3.0%)		
Mixed, urgency predominant	43 (22.1%)		17 (25.4%)		
Previous treatment for UI		195		66	**0.012 (X^2)**
None	137 (70.3%)		57 (86.4%)		
Pessary	1 (0.5%)				
Physical therapist	57 (29.2%)		9 (13.6%)		
Incontinence severity					
ICIQ-UI SF score	9.8 ± 3.1	194	10.1 ± 3.7	65	0.324 (-0.604 to 1.252)

Characteristics	Available at FU	N*	Loss to FU	N*	Difference (95%CI) or p-value
ICIQ-LUTSqol score	33.2 ± 7.4	194	35.0 ± 9.5	65	1.794 (-0.466 to 4.054)
UI (per day)	1.0 (0.33–2.16)	194	0.83 (0.33–3.08)	65	0.321 (U-statistic)

Values are means ± standard deviation, numbers (%), or medians (interquartile range). *Explanation differences in N: missing data of one baseline assessment and three baseline questionnaires. Educational level was assessed at follow-up. Abbreviations: ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; ICIQ-LUTSqol, ICIQ lower urinary tract symptoms quality of life; UI, urinary incontinence.

Appendix table E3: Per protocol study sample baseline characteristics of participants assigned to App-based treatment or care-as-usual

Characteristics	App-treatment	N	Care as usual	N
Age, (years)	54.2 ± 12.4	96	53.0 ± 9.4	75
Body mass index (kg/m2)	26.6 ± 4.7	96	28.1 ± 5.5	75
Higher educational level	52 (54.2%)	96	37 (49.3%)	75
Vaginal births, ≥1	84 (87.5%)	96	63 (84.0%)	75
Postmenopausal status, yes	48 (50.0%)	96	38 (50.7%)	75
Recruitment type		96		75
General practitioner	52 (54.2%)		40 (53.3%)	
Lay press or social media	44 (45.8%)		35 (46.7%)	
Duration of UI (years)	9.5 (5–15)	96	8.0 (4–18)	75
Type of UI		96		75
Stress	35 (36.5%)		30 (40.0%)	
Mixed, stress predominant	26 (27.1%)		22 (29.3%)	
Urgency	11 (11.5%)		7 (9.3%)	
Mixed, urgency predominant	24 (25.0%)		16 (21.3%)	
Previous treatment for UI		96		75
None	70 (72.9%)		49 (65.3%)	
Physical therapist	26 (27.1%)		26 (34.7%)	
Incontinence severity				
ICIQ-UI SF score	9.2 ± 2.9	96	10.7 ± 3.1	75
ICIQ-LUTSqol score	33.0 ± 7.5	96	34.2 ± 7.4	75
UI (per day)	1.0 (0.33–2.00)	96	1.3 (0.50–2.33)	75

Values are means ± standard deviation, numbers (%), or medians (interquartile range).. Educational level was assessed at follow-up. Abbreviations: ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; ICIQ-LUTSqol, ICIQ lower urinary tract symptoms quality of life; UI, urinary incontinence.

Appendix table E4: Unadjusted differences (95% CI) for the change of mean (SD) questionnaire scores from baseline to follow-up

Outcomes	Adjusted difference (95% CI)	Unadjusted difference (95% CI)
ICIQ-UI SF score	0.058 (-0.776 to 0.891)	0.401 (-0.464 to 1.266)
ICIQ-LUTS-qol score	-0.566 (-2.035 to 0.902)	-0.552 (-2.158 to 1.055)

Analyses performed on an intention to treat base without adjustment for baseline scores for the ICIQ-UI SF score and ICIQ-LUTS-qol score. Values are presented as means ± standard deviation or as numbers (%). Abbreviations: ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; ICIQ-LUTS-qol, ICIQ lower urinary tract symptoms quality of life; UI, urinary incontinence.

Appendix table E5: Per protocol analysis for the change of mean UI severity (SD) from baseline to follow up per group allocation and adjusted difference (95% CI)

Outcomes	Change from baseline				Adjusted difference (95% CI)
	App-treatment	N	Care as usual	N	
ICIQ-UI SF score	-2.15 ± 2.56	95*	-2.75 ± 3.62	75	0.071 (-0.837 to 0.979)

Analyses performed on a per protocol base. ICIQ-UI SF score adjusted for baseline. Values are presented as means ± standard deviation. Abbreviations: ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; *One baseline-questionnaire missing.

CHAPTER 5

Cost-Effectiveness Of An App-Based Treatment For Urinary Incontinence In Comparison To Care As Usual In General Practice: A Pragmatic Randomised Controlled Trial Over 12 Months

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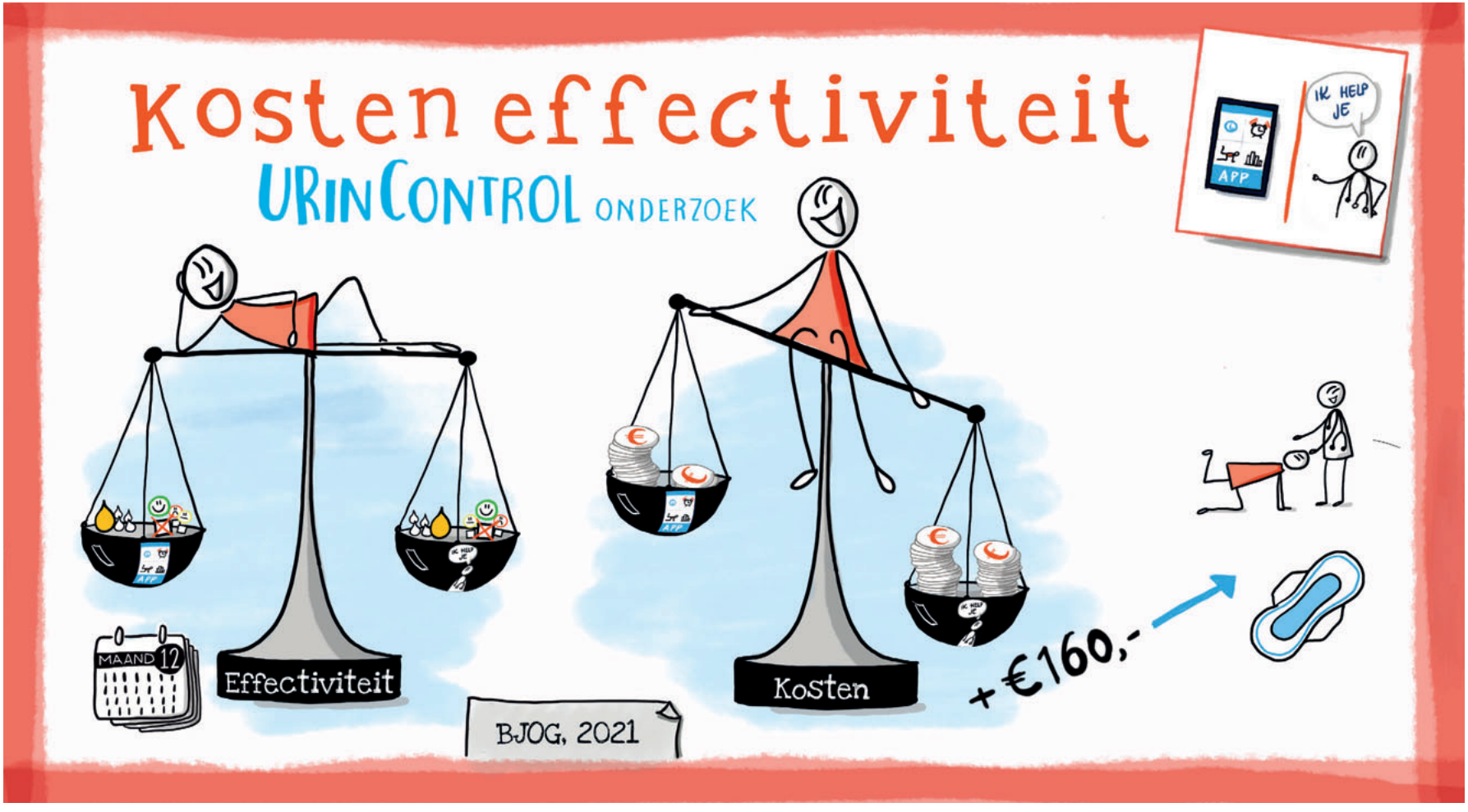
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ABSTRACT

Objective: Long-term cost-effectiveness of app-based treatment for female stress, urgency, or mixed urinary incontinence (UI) compared to care-as-usual in primary care.

Design: A pragmatic, randomised controlled, superiority trial.

Setting: Primary care in the Netherlands from 2015 to 2018, follow-up at 12 months.

Population: Women with ≥2 UI-episodes per week, access to mobile apps, wanting treatment. 262 women randomised equally to app or care-as-usual; 89 (68%) and 83 (63%) attended follow-up.

Methods: The standalone app included conservative management for UI with motivation aids (e.g., reminders). Care-as-usual delivered according to the Dutch GP guideline for UI.

Main outcome measures: Effectiveness assessed by the change in symptom severity score (ICIQ-UI-SF) and the change in quality of life (ICIQ-LUTS-QoL, EQ-5D-5L) on superiority with linear regression on an intention-to-treat basis. Cost-effectiveness and -utility from a societal perspective, based on Incontinence Impact Adjusted Life Years (IIALYs) and Quality Adjusted Life years (QALYs).

Results: Clinically relevant improvement of UI severity for both app (-2.17 ± 2.81) and care-as-usual (-3.43 ± 3.6), with a non-significant mean difference of 0.903 (-0.66 to 1.871). Costs were lower for app-based treatment with €-161 (95%CI: -180 to -151) per year. Cost-effectiveness showed small mean differences in effect for IIALY (0.04) and QALY (-0.03) and thus larger ICER (-3,696) and ICUR (€6,379).

Conclusion: App-based treatment is a viable alternative to care-as-usual for UI in primary care in terms of long-term cost-effectiveness.

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INTRODUCTION

Urinary incontinence (UI) affects one in three women and causes a loss of quality of life. This is compounded by the fact that many women experience barriers to seeking help[1] and often receive suboptimal care when they seek care from a general practitioner (GP).[2,3] These factors can lead both to avoidable suffering if symptoms persist and to unnecessarily high costs for society when inadequate treatment results in limited benefit.

An eHealth application for the treatment of incontinence may not only improve care but also reduce costs by offering an accessible and effective standalone strategy. For this reason, we have developed an app to guide the treatment of women with stress, urgency, and mixed UI. Although digital content and care-as-usual are delivered differently, the content of the app has been carefully designed to reflect that of relevant Dutch and International guidelines for pelvic floor muscle training (PFMT) and bladder training. [4,5] In a qualitative study, we showed that this digital approach to content delivery and treatment was appreciated by women who reported that they expected it to help lower barriers to seeking help, increase self-awareness, and provide support with treatment adherence.[6] Subsequently, in a pragmatic randomised controlled trial, we also confirmed the short-term effectiveness of app-based treatment compared to care-as-usual for treating UI in general practice over 4 months.[7] In that research, app-based treatment was not inferior to care-as-usual and both treatments produced clinically significant decreases in the severity of incontinence, consistent with the results of two Swedish trials showing the effectiveness of an internet-based programme and mobile app for treating stress UI.[8,9] These also reported on the cost-effectiveness of their approach for stress UI compared to postponed treatment or a postal-based programme.[10,11]

The long-term effectiveness and cost-effectiveness of an eHealth application for all common types of UI have not been compared to care-as-usual. However, such a comparison is important if we are to decide whether large-scale implementation is worthwhile from a societal perspective. In the current study, we therefore aimed to assess the long-term effectiveness, costs, and cost-effectiveness of our app-based treatment compared to care-as-usual by GPs.

METHODS

Study design

We performed a pragmatic, parallel arm, randomised controlled trial of patients with stress, urgency, or mixed UI to compare app-based treatment and care-as-usual in a general practice setting. The study design, recruitment challenges, and the primary outcome (non-inferiority of treatment after 4 months) have been published in detail elsewhere.[7,12,13] In this report, we perform a secondary superiority analysis with a focus on the cost-effectiveness after 12 months.

We recruited adult Dutch women with stress, urgency or mixed UI via general practices, the lay press, and social media from July 2015 through July 2018. The full inclusion and exclusion criteria are presented in Appendix A. A baseline assessment was performed by a researcher/GP trainee (AMML and NJW), with participants asked to complete web-based questionnaires and a 3-day frequency-volume chart. Women then underwent a physical and urogynecological examination.[14] The questionnaires and frequency-volume chart were repeated after 4 and 12 months.

Randomization and blinding

A researcher/GP trainee confirmed eligibility, gained signed informed consent, collected baseline data, and enrolled the participant in the study. Randomization was performed using the computer program ALEA, which allowed full concealment of group allocation.[23] Participants were randomised with 1:1 allocation and random block sizes stratified at the GP level.[12] The study design meant that we could not blind participants or care providers to treatment allocation.

Interventions

The details of the interventions are outlined in Appendix A. Women in the intervention group gained access to the URinControl App, the content of which was based on relevant Dutch GP and international guidelines for treating UI.[4,5] Women in the care-as-usual group were referred to their own GP to discuss treatment options. GPs were advised to follow the Dutch GP guideline on UI, without limitations on the type and mode of treatment.[4]

Outcomes

Treatment effectiveness after 12 months was assessed by the change in incontinence symptom severity scores, measured by the International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form (ICIQ-UI-SF), the condition-specific quality of life (ICIQ-LUTSqol), and the five-level version of the EuroQol health status measure (EQ-5D-5L).[15-17] The minimum important differences for the change of score within the treatment groups have been established at 2.52 (SD2.56) for the ICIQ-UI-SF and 3.71 (SD 4.69) for the ICIQ-LUTSqol.[18] A minimum important difference for the EQ-5D-5L was previously established at 0.04 amongst adults with type 2 diabetes.[19]

Costs were measured at a patient level at both 4 and 12 months based on enquiries about medical and non-medical consumption and productivity over the past 4 months. We used the adapted iMCQ and iPCQ questionnaires from the institute of Medical Technology Assessment and included the costs of app development and maintenance. We doubled the costs measured at 12 months to estimate costs between 4 and 12 months. We rated cost components collected during the trial based on the standard Dutch guideline for economic evaluations composed by the Dutch National Health Care Institute.[21] The sum of costs was

recorded as the total societal cost. All costs are presented in euros based on the 2017 year-end prices (2014 prices indexed to inflation by 2.414%). Yearly costs for app development and maintenance were based on the actual costs. A scenario of 30,000 users was used, derived as a conservative estimate from the number of users of freely available apps for UI and on the number of downloads of the Swedish Tät app.[22]

For the cost analysis, effectiveness was measured with the Incontinence Impact Adjusted Life Years (IIALY) score derived from the ICIQ-UI-SF symptom score.[20] The IIALY score reflects disease-specific quality of life weighted from the patient's perspective with a score from 0 (severe impact of UI on quality of life) to 1 (no impact of UI on quality of life). Utility was based on the EQ-5D-5L, with valuations generated using the Dutch tariff for the EQ-5D.[17] The EQ-5D questionnaire is a generic quality of life questionnaire that generates preference-based scores from -0.33 (severe problems on all five dimensions) to 1 (best possible health state). Areas under the receiver operating characteristic curve were used to calculate the IIALYs and QALYs gained for each individual during the 12-month follow-up period: to gain one IIALY or one QALY at a population level (i.e. to add one additional life year in perfect health), the calculated amount (in euros) would need to be invested.

Statistical methods

We assessed treatment effect for superiority between groups by linear regression on an intention to treat basis, with results considered statistically significant if the p-value was <0.05. We compared baseline characteristics of the final cohort with those of the group lost to follow-up with linear regression and non-parametric tests. Data were analysed with IBM SPSS version 26.0 (IBM Corp., Armonk, NY) and R Studio version 1.2.5033.

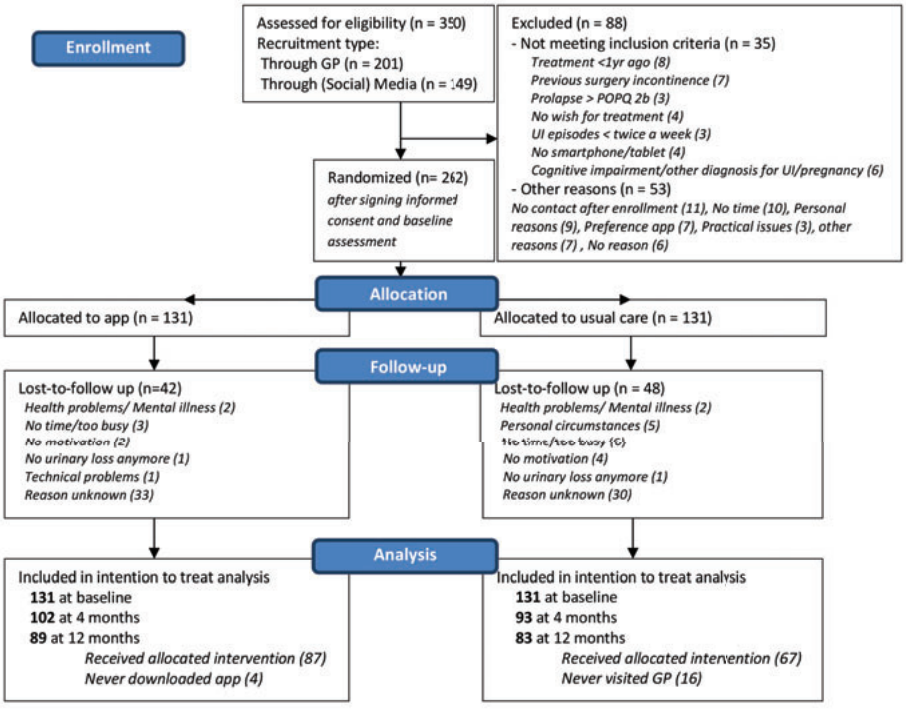
The economic evaluation was conducted from a societal perspective, including direct and indirect medical and non-medical costs over 12 months. Incremental costs per IIALY gained were expressed as an Incremental Cost-Effectiveness Ratio (ICER). The balance between costs and QALYs were expressed as an Incremental Cost-Utility Ratio (ICUR).[21] Costs and effects were recorded and calculated on an individual basis, then the mean differences between the two study groups were calculated. The ICER and ICUR represent the average incremental cost needed to be invested to achieve 1 additional unit of the measure of effect and were computed by dividing the differences in mean effects and mean costs (as shown in Appendix A). By performing 5,000 bootstrap replications of the trial data, alternative confidence intervals were calculated based on the 2.5^{th} and 97.5^{th} centiles. Cost-effectiveness planes visualise the uncertainty surrounding the ICER and ICUR. If the app-based treatment saved costs and differences in effects to be minimal, we would not construct an acceptability curve to assess the probability of cost-effectiveness, as this would already imply accurate cost-effectiveness based on the difference in costs.

Additionally, we performed a sensitivity analysis for a scenario with higher costs for app maintenance and extra costs for annual development. Data robustness was assessed by using the mean of the follow-up data at 4 and 12 months to estimate costs between 4 and 12 months. Finally, we performed subgroup analyses with the type of recruitment or type of UI.

RESULTS

In total, 262 eligible women were randomly allocated to app-based treatment (n = 131) or care-as-usual (n = 131) (Figure 1).

Figure 5.1. Flow diagram of participant recruitment



The mean age of the included women was 54 years (range 23–86 years) and most (66%, n = 114) had moderate UI.[15] Stress UI and more severe UI were more common in the care-as-usual group, despite randomization (Table 1). The 12-month follow-up period ended on 23 September, 2019, by which point 89 women (68%) from the app-based treatment group and 83 (63%) from the care-as-usualgroup were available for the intention to treat analysis.

Table 1. Baseline characteristics of women with complete follow up data shown by treatment group

Characteristics	App-treatment	N*	Care-as-usual	N*
Age, (years)	54.9 ± 12.2	89	52.0 ± 9.8	83
Higher educational level	43 (51.8%)	83	40 (50.6%)	79
Body mass index (kg/m²)	26.6 ± 5.0	89	28.0 ± 5.4	83
Duration of UI (years)	8 (4–14)	89	8 (4–14)	83
Type of UI		89		83
Stress	34 (38.2%)		36 (43.4%)	
Mixed, stress predominant	24 (27.0%)		23 (27.7%)	
Urgency	9 (10.1%)		8 (9.6%)	
Mixed, urgency predominant	22 (24.7%)		16 (19.3%)	
Incontinence severity				
ICIQ-UI SF score	9.2 ± 3.0	88	10.5 ± 3.1	83
ICIQ-LUTSqol score	33.1 ± 7.5	88	33.4 ± 7.2	83
Generic quality of life score (EQ-5D-5L)	0.864 ± 0.19	88	0.896 ± 0.17	83
Makes use of incontinence products, yes	69 (80.2%)	86	68 (84.0%)	81
If yes, mean number of products per day	2 (1–4)	69	2 (1–3.75)	68
Previous treatment for UI		89		83
None	67 (75.3%)		58 (69.9%)	
Pessary	–		1 (1.2%)	
Physical therapist	22 (24.7%)		24 (28.9%)	

* N varied because of missing data of one baseline assessment and three baseline questionnaires.
Values are means ± standard deviation, numbers (%), or medians (interquartile range).
Educational level was assessed at follow up.
Abbreviations: ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; ICIQ-LUTSqol, ICIQ lower urinary tract symptoms quality of life; UI, urinary incontinence.

Treatment groups

Supplemental table S1 shows the interventions received by both treatment groups. Loss to follow-up in both treatment groups was associated with younger age and higher body mass index, we found no other significant differences between the groups (Supplemental table S2). We chose not to impute any values because the group with follow-up data was representative and few data were missing.

Effectiveness

Both app-based treatment and care-as-usual showed improvements of all symptom scores after 12 months (Supplemental table S3). Severity of incontinence improved with respectively -2.17 (SD 2.8) versus -3.43 (SD 3.6) points, the change in condition-specific quality of life improved with respectively -4.66 (SD 5.1) versus -4.34 (SD 5.7) and generic quality of life improved with respectively 0.021 (SD 0.17) versus 0.0008 (SD 0.14) points. However, there were no statistically significant differences in the change in symptom scores between treatment groups (Supplemental table S4). After 12 months, women gained an average 0.71 IIALYs in the intervention group and 0.66 IIALYs in the care-as-usualgroup (Table 2). In addition, women gained an average of 0.89 QALYs in the app-based treatment group and 0.91 QALYs in the care-as-usualgroup, equating to respective gains of 0.89 and 0.91 years in perfect (incontinence-specific) health.

Costs

The mean direct and indirect cost per participant in the app-based treatment group was €1,520 (95% CI: 1,512–1,532), including €87 (95% CI: 85–86) for UI-specific costs. The mean direct and indirect cost per participant in the care-as-usual group was €1,680 (95% CI: 1,673–1,693), including €191 (95% CI: 192–195) for UI-specific costs (Supplemental table S5). For both the app-based treatment and care-as-usual groups, incontinence material drove much of the UI-specific costs (€62 and €80, respectively). Compared with app-based treatment, care-as-usual was associated with higher costs for physical therapy, medication, and other treatments for UI, equating to mean differences of €82, €9, and €8 per patient per year, respectively. The cost of app-usage was €1.10 per patient per year based on the scenario of 30,000 users.

Cost-effectiveness and cost-utility analyses

The cost-effectiveness analysis showed that the mean difference in effect gained per IIALY was 0.043 more for app-based treatment than for care-as-usual. The mean difference in costs was €161 less (95% CI: -180 to -151) in the app-based treatment group, giving an ICER of -€3,696 (95% CI: -6,716 to 12,712). The cost-utility analysis revealed that there was a mean difference of -0.025 QALYs (i.e. fewer) for app-based treatment compared with care-as-usual, with an ICUR of €6,379 (95% CI: -4,128 to 21,769) (Table 2 and Figure 2).

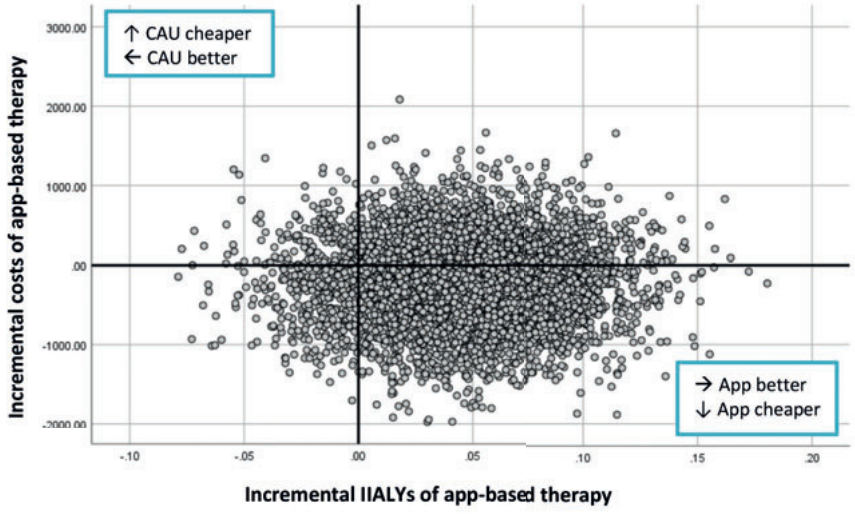
In total, 65.6% of the 5,000 replications in the bootstrap simulation were in the lower half of the plane, indicating lower costs for app-based treatment (Figure 2). Moreover, any effects and utilities gained were comparable, with minimal differences between the groups in either IIALY (0.043) or QALY (-0.025).

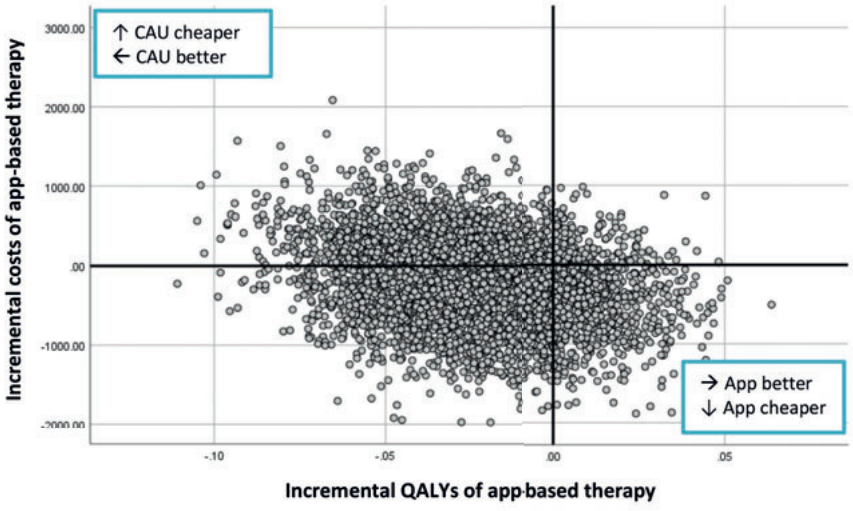
Table 2. Cost-effectiveness of app-based treatment for urinary incontinence for women in general practice

	Treatment Group		Mean difference	
	App-based	Care-as-usual		
	N = 87	N = 82		ICER (95% CI)
IIALYs gained	0.71 ± 0.215	0.66 ± 0.250	0.043	€-3,696 (CI -6,716 to 12,712)
Costs	1,520 ± 3,425	1,680 ± 3,357	-161	
				ICUR (95% CI)
QALYs gained	0.89 ± 0.165	0.91 ± 0.145	-0.025	€6,379 (CI -4,128 to 12,769)
Costs	1,520 ± 3,425	1,680 ± 3,357	-161	

IIALYs, Incontinence Impact Adjusted Life Years; ICER, Incremental Cost Effectiveness Ratio; QALYs, Quality Adjusted Life Years; ICUR, Incremental Cost Utility Ratio. * Three cases were excluded from the analyses because a large influence on the data due to outliers in costs.

Figure H5.2. Incremental cost-effectiveness ratio (ICER) scatterplot for app-based treatment versus care-as-usual.





Sensitivity and subgroup analyses

App-based treatment remained cost-effective when assessed with fewer app users, extra developmental and higher maintenance costs (Supplemental table S6). Sensitivity analysis using the mean costs at 4 and 12 months' follow-up revealed comparable results, demonstrating the robustness of the cost calculation.

Subgroup analysis revealed differences in effects and costs by UI type and recruitment type (Supplemental table S7). App-based treatment for urgency UI resulted in higher IIALYs gained (0.74) compared with care-as-usual (0.60). The costs for UI-specific treatment were also approximately €60 higher for urgency UI compared with stress UI mainly due to the cost of incontinence material. Subgroup analysis by recruitment type showed that, for care-as-usual, the group recruited through (social) media had lower costs (€131) and a lower treatment effect (IIALY 0.64) than the group recruited by a GP (€235, IIALY 0.68). These cost differences were mainly based on lower use of physical therapy (€56 versus €122) and other treatments (e.g. pessary or tension-free vaginal tape) (€2 versus €86).

DISCUSSION

Main Findings

App-based treatment for female stress, urgency, and mixed UI appears to be a cost-effective alternative to care-as-usual in general practice. After 12 months, both treatments produced clinically relevant changes in the main outcome measures that were larger than after 4 months. Indeed, UI symptoms and quality of life measures continued to improve. However, there was no significant difference in change between the two study groups. App-based treatment was less expensive than care-as-usual, with mean differences of €161 and €87 per patient per year in total and UI-specific costs, respectively. The gained effects and utilities were comparable between groups after 1 year, with only small mean differences in the IIALY (0.043) and the QALY(-0.025). This resulted in an ICER of -€3,696 and an ICUR of €6,379. These results were robust and remained valid in a scenario that included higher app development costs.

Strengths and limitations

The main strength of this study is that we compared app-based treatment with care-as-usual. The pragmatic design is considered the gold standard for economic evaluations in health care.[24] Other strengths are the inclusion of all common UI types, the use of patient-centred and validated outcome measures, the 12-month follow-up period, and the inclusion of sensitivity analyses to confirm the robustness of our data.

The cost and effect analyses were sufficient to make valid conclusions about cost-effectiveness. Although the ICER and ICUR are typically used to represent costs associated with 1 unit of health gain, we set the difference to focus on cost rather than health gains given that the latter was comparable between the groups. Consideration of this health gain would be confusing, as the minimal differences result in high ratios of ICER and ICUR.

Limitations that must be considered are power and loss to follow-up. Often, cost-effectiveness studies are underpowered because their power depends on the primary outcome measure of a trial. This trial was powered on non-inferiority of effectiveness after 4 months. In this secondary analysis, 172 women (65.6%) were available for follow-up and power was lower. By performing a bootstrap analysis, this issue does not affect the results of the cost-effectiveness analysis. However, the lower power must be considered in our effectiveness and subgroup analyses. Loss to follow-up was associated with higher body mass index. Participation of these women could have further improved effects and lowered costs for both treatment groups, as weight loss is effective for UI and a cheap intervention.

Interpretation (in light of other evidence)

Our study findings are consistent with those from two other studies concluding that app- or internet-based treatment is a cost-effective alternative when managing UI.[10,11] These studies compared an app-based approach with either a postal-based programme or postponed treatment and assessed their cost-effectiveness for stress UI in superiority trials. However, in any such evaluation, it is recommended to use a pragmatic design with a control group that reflects usual care.[24] Ours is the first study to conduct such a comparison, with the results indicating that app-based treatment is a cost-effective alternative for women with UI who present to general practice.

The UI-specific follow-up costs over 12 months in our data were comparable to other studies, while our total costs were higher for both app-based treatment and care-as-usual (€1520 and €1680, respectively) compared with the data provided by Sjöström et al. (€547 and €482, respectively) and Vermeulen et al. (€417 and €87, respectively).[11, 20] Although all three studies used a societal perspective, we took into consideration a broader range of costs unrelated to UI, for example loss of productivity, to conduct the societal perspective as thorough as possible.

We consider that women recruited to our trial via (social) media represent a cohort that experience barriers to seeking help from a GP. Subgroup analysis showed that for care-as-usual, the effects and costs were lower for women recruited through (social) media. These women did visit their GP to discuss treatment options just as often, but received PFMT less often (31% compared to 50%). This leads us to question if women who experience barriers to seeking help also experience barriers to accepting help when it is offered. It is conceivable that women in this cohort prefer treatment without professional involvement, which would bring the role of app-based treatment and the importance of access via (social) media to the fore.

Our subgroup analysis showed that app-based treatment for urgency UI had higher treatment effects on the impact of incontinence on daily life (0.74 IIALYs) than did care-as-usual for urgency UI (0.60 IIALYs). This may result from the accessibility of the app, which helps women to distract from feelings of urgency and to monitor the bladder training (e.g. the pee button). The treatment of urgency UI with an eHealth approach has not been studied before, precluding meaningful comparison.

CONCLUSION

Practical recommendations

With these results, we believe App-based treatment can be recommended as a viable alternative to care-as-usual in general practice. Furthermore, we expect that its implementation will lower barriers to seeking and receiving help for UI because it can be used either as a standalone option or as a tool in blended care (supporting care-as-usual). Although GPs or pelvic physical therapists can offer the app to women who seek help for UI, there is scope for it to be promoted through (social) media and offered online, allowing it to reach cohorts that may not otherwise seek care.

Research recommendations

It will be important to identify the factors associated with treatment success and failure if we are to ensure successful implementation and treatment efficacy. Indeed, clarifying these factors could help to improve the app's content and to ensure that it targets the most appropriate populations. Mixed-methods research could be of benefit,[25] and as such, we are currently preparing a report that combines our quantitative and qualitative results. Additionally, it will be important to evaluate and improve the implementation process continuously by collecting user feedback and evaluating log data.

We conclude that the app-based treatment for stress, urgency, and mixed female UI is a cost-effective alternative to care-as-usual in general practice after 12 months. App-based treatment can therefore be recommended as a viable alternative to care-as-usual in general practice.

REFERENCES

1. Visser E, De Bock GH, Kollen BJ, Meijerink M, Berger MY, Dekker JH. Systematic screening for urinary incontinence in older women: Who could benefit from it? Scand J Prim Heal Care. 2012;30:21–8.
2. Van Gerwen MAG, Schellevis FG, Lagro-Janssen ALM. Management of urinary incontinence in general practice: Data from the second Dutch national survey. J Eval Clin Pract. 2009;15(2):341–5.
3. Minassian VA, Yan X, Lichtenfeld MJ, Sun H, Stewart WF. The iceberg of health care utilization in women with urinary incontinence. Int Urogynecol J. 2012; 23:1087–1093.
4. Damen-van Beek Z, Wiersma T. Practice guideline 'Urinary incontinence in women' from the Dutch College of General Practitioners. Ned Tijdschr Geneeskd. 2016;160:D674.
5. Abrams P, Andersson K-E, Apostolidis A, Birder L, Bliss D, Brubaker L, et al. 6th International Consultation on Incontinence. Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence. Neurourol Urodyn. 2018 Sep;37(7):2271–2.
6. Wessels NJ, Hulshof L, Loohuis AMM, van Gemert-Pijnen L, Jellema P, van der Worp H BM. User experiences and preferences regarding an app for the treatment of urinary incontinence in adult women: a qualitative study. JMIR Mhealth Uhealth 2020;8(6):e17114.
7. Loohuis AMM, Wessels NJ, Dekker JH, van Merode NAM, Slieker-ten Hove MC, Kollen BJ, Berger MY, van der Worp H BM. App-based treatment for urinary incontinence non-inferior to care-as-usual in primary care. Results of a pragmatic, randomized controlled trial. Ann Fam Med. 2020;(In press).
8. Sjöström M, Umefjord G, Stenlund H, Carlbring P, Andersson G, Samuelsson E. Internet-based treatment of stress urinary incontinence: 1- and 2-year results of a randomized controlled trial with a focus on pelvic floor muscle training. BJU Int. 2015;116(6);955-964
9. Asklund I, Nyström E, Sjöström M, Umefjord G, Stenlund H, Samuelsson E. Mobile app for treatment of stress urinary incontinence: A randomized controlled trial. Neurourol Urodyn. 2017;36(5):1369–76.
10. Sjöström M, Umefjord G, Lindholm L, Samuelsson E. Cost-effectiveness of an Internet-based treatment program for stress urinary incontinence. Neurourol Urodyn. 2015;34(3):244–50.
11. Sjöström M, Lindholm L, Samuelsson E. Mobile app for treatment of stress urinary incontinence: A cost-effectiveness analysis. J Med Internet Res. 2017;1;19(5).
12. Loohuis AM, Wessels NJ, Jellema P, Vermeulen KM, Slieker-ten Hove MC, van Gemert-Pijnen JE, et al. The impact of a mobile application-based treatment for urinary incontinence in adult women: Design of a mixed-methods randomized controlled trial in a primary care setting. Neurourol Urodyn. 2018;37:2167–76.
13. van der Worp H, Loohuis AMM, Flohil IL, Kollen BJ, Wessels NJ, Blanker MH. Recruitment through media and general practitioners resulted in comparable samples in an RCT on incontinence. J Clin Epidemiol. 2020;1;119:85–91.
14. Bump R, Mattiasson A, Bo K, Brubaker L, DeLancey J, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obs Gynecol. 1996;175(1):10–17.
15. Klovning A, Avery K, Sandvik H, Hunskaar S. Comparison of two questionnaires for assessing the severity of urinary incontinence: The ICIQ-UI SF versus the Incontinence severity index. Neurourol Urodyn. 2009;(28):411–5.
16. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: A brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn. 2004;23(4):322–30.

17. Versteegh M, M. Vermeulen K, M. A. A. Evers S, de Wit GA, Prenger R, A. Stolk E. Dutch Tariff for the Five-Level Version of EQ-5D. Value Heal. 2016;19(4);343-352.
18. Nystrom E, Sjostrom M, Stenlund H, Samuelsson E. ICIQ symptom and quality of life instruments measure clinically relevant improvements in women with stress urinary incontinence. Neurourol Urodyn. 2015;34(8):747–51.
19. McClure NS, Sayah F Al, Ohinmaa A, Johnson JA. Minimally Important Difference of the EQ-5D-5L Index Score in Adults with Type 2 Diabetes. Value Heal [Internet]. 2018;21(9):1090–7.
20. Vermeulen KM, Visser E, Messelink EJ, Schram AJ, Berger MY, de Bock GH DJ. Cost-effectiveness of a pro-active approach of urinary incontinence in women. BJOG An Int J Obstet Gynaecol. 2016;123(7):1221.
21. Zorginstituut Nederland. Guideline for conducting economic evaluations in healthcare [in Dutch: Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg]. 2016.
22. Loohuis A, Chavannes N. Medical apps; Care for the future? [Dutch]. Huisarts Wet. 2017;60:440–3.
23. ALEA software for randomization in clinical trials. http://tenalea.net/Documents/ALEA/ALEARandomizationProgramFeatures.pdf.
24. Drummond, M.E., Sculpher, M.J., Torrance G. Methods for The Economic Evaluation of Health Care Programmes. 3rd edition. Oxford, UK: Oxford University Press; 2005
25. Ivankova N V., Creswell JW, Stick SL. Using Mixed-Methods Sequential Explanatory Design: From Theory to Practice. Field methods. 2006;18(1):3–20.

SUPPLEMENTAL MATERIAL

Supplement A. Supplemental Methods

Full inclusion and exclusion criteria

We used the following inclusion criteria: female sex; age ≥18 years; self-reported stress, urgency, or mixed UI at least twice a week according to the Three Incontinence Questions (3IQ); wanting treatment; and access to a smartphone or tablet. Women were excluded if they had any of the following: indwelling urinary catheter, urogenital malignancy, previous surgery for UI, treatment for UI in the previous year (pharmacological or non-pharmacological), terminal or serious illness, cognitive impairment, psychiatric illness, urinary tract infection (by dipstick, and if negative, by dip slide or urine culture), overflow or continuous UI, pregnancy or recent childbirth (<6 months ago), or the inability to complete a questionnaire in Dutch.

Interventions

App-based treatment group

Women in the intervention group gained access to the URinControl App, the content of which was based on relevant Dutch GP and international guidelines for treating UI.[4,5] This includes information about UI, a programme for self-managing UI, and reminders and graphs to improve treatment adherence. For urgency UI, the app has a "pee button" that can be used to track the time between two urinations and has distraction games to help suppress the feelings of urgency. Participants received a personal account and instructions to download and install the app on a smartphone or tablet. After randomization, the research team provided technical support only. However, each participant was free to contact her GP with any questions about UI or to receive additional treatment.

Care-as-usual group

Participants in the care-as-usual group were referred to their own GP to discuss treatment options. GPs were advised to follow the Dutch GP guideline on UI, without limitations on the type and mode of treatment.[4] Care-as-usual could consist of any of the following, alone or in combination: instructions on PFMT and/or bladder training; prescribing a pessary, drugs, or absorbent products; referral to a continence nurse, a pelvic physical therapist, or to secondary care (e.g. a urogynaecologist). GPs were not informed about the content of the app, and the participants received no additional information on UI from the researchers.

Incremental cost-effectiveness and cost-utility ratio calculation

$$\text{ICER} = \frac{\text{(Costs of app-based treatment – Costs of care-as-usual)}}{\text{(Effect of app-based treatment – Effect of care-as-usual)}}$$

$$\text{ICUR} = \frac{\text{(Costs of app-based treatment – Costs of care-as-usual)}}{\text{(Utility of app-based treatment – Utility of care-as-usual)}}$$

Costs, effects, and utilities are reported as means per patient per year.

Details of Participant Involvement

Ten patients tested the app for usability, and caregivers (urologist, gynecologist, pelvic floor physical therapist, general practitioner) were involved in the development phase before the trial.[12] Alongside the trial, we further evaluated the experiences and preferences of patients and caregivers.[6] We asked participating practices for feedback on trial logistics and we sent frequent updates. The study participants were offered the opportunity to hear the results of the study upon completion to help with the dissemination of results. To inform the general public, we have provided plain-language summaries in text, infographics, and videos via social media and our website (www.urincontrol.nl).

Supplemental Table S1. Comparison of groups by interventions received at both follow-up assessments

	0–4 months		4–12 months (8–12)	
	App n = 102 (77.9%)	**CAU n = 93 (71.0%)**	**App n = 89 (68%)**	**CAU n = 83 (63.3%)**
Received allocated intervention (App-login or visited GP at least once)	96 (94.1)	75 (80.6)	87 (97.7)	67 (80.7)
Specific treatment for UI				
Physical therapy for UI	6 (5.9)	36 (38.7)	3 (3.4)*	15 (18.1)**
Medication from GP for UI	2 (2.0)	3 (3.2)	–	3 (3.6)***
Physical therapy and Medication from GP	–	–	–	–
Alternative medication for UI	–	–	–	–
Physical therapy and Medication from GP	–	1 (1.1)	–	–
Medication from GP or alternative medication	2 (2.0)	–	–	–
Physical therapy, Medication from GP, and alternative medication	–	1 (1.1)	–	–
Other treatment: referral to website by GP (1)/ continence nurse (2)/pessary (1)/TVT (1)	–	3 (3.2)	–	2 (2.4)

* One patient also received physical therapy in the first 4 months. ** Eleven patients also received physical therapy in the first 4 months. Four were lost to follow up at 12 months. ***All patients also received medication at 4 months

Supplemental Table S2: Comparison of baseline characteristics between patients followed up and patients lost to follow up at 12 months

Characteristics	Available at FU	N*	Loss to FU	N*	Difference (95%CI) or p-value
Age, (years)	53.5 ± 11.2	172	49.9 ± 12.2	90	**-3.164 (-6.570 to -0.657)**
Body mass index (kg/m²)	27.3 ± 5.2	172	28.7 ± 5.4	89	**1.516 (0.155 to 2.878)**
Higher educational level	83 (51.2%)	162	18 (54.5%)	33**	
≥1 Vaginal births	143 (83.1%)	172	73 (82.0%)	89	0.241 (X^2)
Postmenopausal status, yes	88 (51.2%)	172	35 (39.3%)	89	0.145 (X^2)
Recruitment type		172		90	0.631 (X^2)
General practitioner	96 (55.8%)		56 (62.2%)		
Lay press or social media	76 (44.2%)		34 (37.8%)		
Duration of UI (years)	8.0 (4–14)	172	7.0 (3.3–15.0)	89	0.613 (U-statistic)
Type of UI		172		90	0.104 (X^2)
Stress	70 (40.7%)		40 (44.4%)		
Mixed, stress predominant	47 (27.3%)		23 (25.6%)		
Urgency	17 (9.9%)		5 (5.6%)		
Mixed, urgency predominant	38 (22.1%)		22 (24.4%)		
Previous treatment for UI		172		89	0.452 (X^2)
None	125 (72.7%)		69 (77.5%)		
Pessary	1 (0.6%)				
Physical therapist	46 (26.7%)		20 (22.5%)		
Incontinence severity					
ICIQ-UI SF score	9.8 ± 3.1	172	10.0 ± 3.6		0.192 (-0.658 to 1.043)
ICIQ-LUTSqol score	33.3 ± 7.4	172	34.4 ± 9.2		1.129 (-0.945 to 3.203)
Use of Incontinence pads, yes	137 (82.0%)	167	72 (81.8%)	88	0.966 (X^2)

Values are means ± standard deviation, numbers (%), or medians (interquartile range). *Explanation differences in N: missing data of one baseline assessment and three baseline questionnaires. **Educational level was assessed at follow up after 4 months. Abbreviations: ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; ICIQ-LUTSqol, ICIQ lower urinary tract symptoms quality of life; UI, urinary incontinence.

Supplemental Table S3. Questionnaire scores at baseline and follow up comparing app-based treatment and care-as-usual

Outcomes	Questionnaire scores					
	App-based treatment			Care-as-usual		
	Baseline	4 mo.	12 mo.	Baseline	4 mo.	12 mo.
	N = 130	N = 102	N = 89	N = 129	N = 93	N = 83
UI-SFa	9.54 ± 3.2	7.11 ± 3.1	7.00	10.3 ± 3.4	7.8 ± 4.0	7.1 ± 4.3
LUTSqolb	33.9 ± 8.3	28.8 ± 6.5	28.4 ± 6.9	33.4 ± 7.8	29.4 ± 8.0	29.1 ± 8.0
EQ-5D-5Lc	0.86 ± 0.19	0.90 ± 0.17	0.89 ± 0.18	0.89 ± 0.16	0.93 ± 0.13	0.90 ± 0.16

All data are shown as Mean ± SD and on an intention to treat basis. Follow up was after 4 and 12 months.
Abbreviations: ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; ICIQ-LUTS-qol, ICIQ lower urinary tract symptoms quality of life; EQ-5D-5L, EuroQol health status measure five-level dimension. *Two and one baseline-questionnaire missing.
[a]Range, 0–21; higher scores correlate with worse incontinence.
[b]Range, 19–76; higher scores correlate with a greater negative impact of incontinence on quality of life.
[c]Range, -0.333 to 1.0; a weighted health state index, with higher scores correlating with higher quality of life.

Supplemental Table S4. Change in questionnaire scores from baseline to 12 months by treatment group, including the adjusted difference between groups

Outcomes	Change in score from baseline		Adjusted difference (95% CI)
	App-based treatment N = 88	Care-as-usual N = 83	
ICIQ-UI SF score	-2.17 ± 2.81	-3.43 ± 3.6	0.903 (-0.66 to 1.871)
ICIQ-LUTSqol score	-4.66 ± 5.1	-4.31 ± 5.70	0.445 (-1.125 to 2.015)
EQ-5D-5L score	0.021 ± 0.17	0.008 ± 0.14	0.001 (-0.041 to 0.043)

Values are presented as mean ± standard deviation. Analyses were performed on an intention to treat basis. All outcome measures and difference were adjusted for baseline scores.
Abbreviations: ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; ICIQ-LUTSqol, ICIQ lower urinary tract symptoms quality of life; EQ-5D-5L, EuroQol health status measure five-level dimension.

Supplemental table S5. Mean costs per participant for app-based treatment and care-as-usual for women with urinary incontinence

Outcomes	Unit costs (€)	Mean costs		Mean difference	(95% CI)
		App group (n = 89)	Care-as-usual (n = 83)		
UI specific costs					
Physical therapy for UI	€33/ consultation*	11.65	93.97	-82.32	(-83.55 to -82.38)
Medication for UI	Price/drug**	0	8.66	-8.66	(-8.71 to -8.47)
Other treatment for UI	Incontinence nurse /pessary/ TVT	0	8.28	-8.28	(-8.24 to -7.98)
Acupuncture for UI	€65/treatment*	11.20	0	11.20	(10.87 to 11.49)
Incontinence pads	Price/type pad	62.93	79.63	-16.71	(-22.09 to -19.03)
App Development	€30000* in total	1.0	0	1.0	–
App Maintenance	€3000*/year	0.1	0	0.1	–
Subtotal UI specific costs		**86.89**	**190.55**	**-103.66**	**(-111.44 to -107.42)**
UI-unrelated healthcare costs					
First-line services					
General practitioner	€33/ consultation*	113.43	100.57	12.87	(11.93 to 13.04)
Social services	€65/ consultation*	9.95	27.60	-17.65	(-18.10 to -17.18)
Ergotherapist	€33/ consultation*	9.32	7.42	1.90	(1.73 to 2.12)
Logopedist	€30/ consultation*	0	0	0	–
Dietist	€25/ consultation*	10.91	11.59	-0.66	(-0.85 to -0.50)
Homeopath	€65/ consultation*	25.40	11.01	14.31	(13.54 to 14.41)
Psychologist	€79/ consultation*	121.83	131.23	-9.40	(-11.35 to -7.16)
Occupational physician	€138/ consultation*	63.45	55.54	7.9	(6.53 to 8.67)
Domestic help	€20/hour*	2.47	32.97	-30.50	(-31.64 to -30.35)
Personal care	€50/hour*	0	0	0	–
Nursing	€73/hour*	0	0	0	–
Second-line care					
Visit emergency medicine	€259/visit*	36.59	19.41	17.18	(17.10 to 18.15)
Transport by ambulance	€316/transport*	14.43	7.66	6.78	(6.41 to 7.33)
Specialist consultation	€259/visit*	130.69	84.10	46.59	(45.34 to 46.95)

Outcomes	Unit costs (€)	Mean costs		Mean difference	(95% CI)
		App group (n = 89)	Care-as-usual (n = 83)		
Ambulant therapy hospital	€276/treatment*	38.99	96.52	-57.53	(-60.22 to -57.17)
Ambulant revalidation	Price/treatment	2.64	82.88	-80.23	(-83.08 to -79.28)
Admission in hospital	€476/day	56.03	124.84	-62.81	(-72.60 to -68.72)
Admission other institute		0	35.67	-35.67	(-37.05 to -35.06)
Subtotal UI-unrelated healthcare costs		**636.15**	**829.09**	**-192.94**	**(-204.48 to -192.89)**
Other costs					
Travel costs	€0.19/km; €3.00 parking costs***	13.13	14.63	-1.49	(-1.67 to -1.50)
Productivity losses	*	783.54	646.07	137.33	(127.86 to 150.10)
Subtotal other costs		**796.54**	**660.70**	**135.84**	**(126.26 to 148.54)**
Total costs		**1,519.58**	**1,680.34**	**-160.762**	**(-179.88 to -150.96)**

Means and mean differences based on trial data, 95%CI result from bootstrap sample.

* Prices according to Guideline Dutch Healthcare Institute

** Prices according to: Pharmacotherapeutic compass. Price per day by daily usage plus prescription costs of €5.99 per medication per 90 days.

*** Mean travel distances: 1.1km to GP practice, 2.2km to physiotherapist, 7.0 km to specialist

Supplemental table S6. Sensitivity analyses of the Incremental cost-effectiveness ratios

Sensitivity scenarios	N	Means per patient per year				ICER (95%CI)
		Costs*		IIALYs		
		Totals	Difference	Gained	Difference	
Original analysis						
App-based treatment	87	1,520	161**	0.71	0.04	3,620 (-11,852 to 7,577)
Care-as-usual	82	1,680		0.66		
Higher costs app						
App-based treatment	87	1,523	157	0.71	0.04	3,696 (-6,783 to 12,626)
Care-as-usual	82	1,680		0.66		
Robustness data						
App-based treatment	87	1,528	94	0.71	0.04	2,155 (-7,697 to 11,633)
Care-as-usual	82	1,622		0.66		

*Total costs are in euro's per patient per year; IIALY, Incontinence Impact Adjusted Life Years; ICER, Incremental Cost Effectiveness Ratio calculated by the mean difference of total costs/mean difference IIALYs gained; UI = Urinary incontinence.

** Numbers are rounded.

Supplemental table S7. Subgroup analyses of the Incremental cost-effectiveness ratios, including UI-specific costs

Subgroup analyses	N	Means per patient per year				ICER (95%CI)
		Costs* (UI specific)		IIALYs		
		Totals	Difference	Gained	Difference	
Original analysis						
App-based treatment	87	1,520 (87)	161 (104)	0.71	0.04	3,620 (-11,852 to 7,577)
Care-as-usual	82	1,680 (191)		0.66		
UI types						
Stress UI						
App-based treatment	56	1,595 (69)	-374 (105)	0.69	0.001	-374,364 (-364,942 to 126,682)
Care-as-usual	58	1,221 (173)		0.69		
Urgency UI						
App-based treatment	31	1,382 (120)	1,407 (111)	0.74	0.14	10,275 (12,341 to 16,496)
Care-as-usual	24	2,790 (231)		0.60		
Recruitment types						
General practitioner						
App-based treatment	47	1,564 (83)	86 (152)	0.71	0.02	3,754 (-2,088 to 3,624)
Care-as-usual	47	1,650 (235)		0.68		
(Social) Media						
App-based treatment	40	1,468 (92)	253 (39)	0.71	0.07	3,619 (-16,894 to 15,337)
Care-as-usual	35	1,721 (131)		0.64		

CHAPTER 6

A Prediction Model Study Focusing On Ehealth In The Management Of Urinary Incontinence: The Personalized Advantage Index As A Decision-Making Aid

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Voorspellers voor succes
URINCONTROL ONDERZOEK
IK HELP JE
APP
WAT IS GOED VOOR MIJ?
IK HELP JE
APP
Ernst urineverlies
Opleidings-niveau
Leeftijd
Kwaliteit van leven

ABSTRACT

Objective: To develop a prediction model to illustrate how the personalization of treatment decisions affects the choice between app-based treatment and care as usual, focusing on women with stress, urgency, or mixed urinary incontinence (UI) as well as the practical potential of this approach.

Design: A prediction model study using data from a pragmatic, randomized controlled, non-inferiority trial.

Setting: Primary care in the north of the Netherlands from 2015, with social media included from 2017. Enrollment ended in July 2018.

Participants: Adult women were eligible if they had ≥2 episodes of UI per week, access to mobile apps, and wanted treatment. Of the 350 screened women, 262 were eligible and randomized to app-based treatment or care as usual; 195 (74%) attended follow-up. Given the sample size, we required a maximum of 28 parameters to build the model.

Predictors: Literature review and expert opinion identified 13 candidate predictors, which we categorized into two groups: Prognostic factors (independent of treatment type), such as UI severity, postmenopausal state, vaginal births, general physical health status, pelvic floor muscle function, and body mass index; and modifiers (dependent on treatment type), such as age, UI type and duration, impact on quality of life, previous physical therapy, recruitment method, and educational level.

Main outcome measure: The primary outcome of the trial was the symptom severity score after 4 months, measured by the International Consultation on Incontinence Questionnaire the Urinary Incontinence Short Form. Prognostic factors and modifiers were combined into a final prediction model. For each participant, we then predicted treatment outcomes and calculated a personalized advantage index (PAI) before assessing its benefits.

Results: One prognostic factor (baseline UI severity) and three modifiers (age, educational level, and impact on quality of life) independently affected the treatment effect of eHealth in our sample. The mean PAI was 0.99 ± 0.79 points, being of clinical relevance in 21% of individuals. Applying the PAI also significantly improved treatment outcomes at the group level.

Conclusions: Personalizing treatment choice can support treatment decision making between eHealth and care as usual through the practical application of prediction modeling. Concerning eHealth for UI, this could facilitate the choice between app-based treatment and care as usual.

INTRODUCTION

Randomized controlled trials provide evidence of treatment effects at a group level, but they fail to provide the individual-level predictive information needed to optimize treatment in a given patient. This is especially relevant when two treatments show only marginal differences in effect at the group level, as occurs in a non-inferiority design, where the added value of personalized treatment decision might be greater. A prediction model for treatment outcome, based on a patient's individual characteristics, may facilitate the personalization of treatment decisions.[1] Different approaches to the development of clinical decision support tools informed by prediction models have been published in epidemiological and statistical literature, being developed for various disorders.[2-4] In mental healthcare, where treatment options for depression often show comparable effectiveness and marked individual variability, the personalized advantage index (PAI) has shown utility.[4,5] This method predicts individualized outcomes for the treatment received (factual) and its alternatives (counterfactual), with the difference between these called the PAI. In this way, the optimal treatment and the magnitude of its predicted advantage can be quantified for a given patient. The PAI model accounts for patient characteristics that predict outcomes both irrespective of, and interacting with, the type of treatment.

The effectiveness of eHealth is often demonstrated as "non-inferior" to a traditional treatment option, which is considered acceptable because of potential advantages unrelated to effectiveness, such as improved accessibility, privacy, or cost savings.[6] However, treatment responses can vary widely at the individual level even when there is non-inferiority at the group level. For example, we demonstrated that an app-based treatment for female urinary incontinence (UI) was non-inferior to care as usual at a group level, but we equally found that individual outcomes at follow-up varied from "much worse" to "very much better" in both treatment groups.[7] Previously, higher age, treatment expectations, and disease severity were reported to predict better outcomes for UI when using eHealth.[8,9] Although a given patient and caregiver could weigh these separate characteristics when making a treatment decision, it would be much more informative to know what specific outcomes one can expect from the available treatment options. We are unaware of the PAI having been applied to treatment decisions concerning eHealth.

In this study, we used existing RCT trial data to develop a prediction model and illustrate how the personalization of treatment decisions affects the choice between app-based treatment and care as usual. We also studied the practical potential of this approach in women with stress, urgency, or mixed UI. First, we built a prediction model for the outcomes of app-based treatment and care as usual for UI, and we used this to predict outcomes given the actual treatment received (factual) and the hypothetical outcome of the treatment that was not received (counterfactual). Second, we used the PAI to identify the optimal treatment and to quantify its added benefit in individual participants. Third, we assessed the clinical relevance of any benefit and whether using the PAI improved treatment outcomes at the group level.

METHODS

Data source and study design

We used data from the URinControl-trial, a pragmatic, non-inferiority, randomized-control trial of women with stress, urgency, or mixed UI who received either app-based treatment or care as usual via their general practitioner (GP). The trial design, the development and content of the app, and the clinical results have been published previously.[7-9] The original trial reported the non-inferiority of app-based treatment to care as usual at a group level. In the present study, we use these data to build a prediction model, predict treatment outcomes at an individual level, and calculate the PAI.

Participants

Participant enrollment took place from July 2015 through July 2018, with follow-up ending on December 20th, 2018. We recruited participants in the north of the Netherlands via 88 GPs from 31 practices, and through social media and the lay press. Adult women were eligible if they had ≥2 episodes of self-reported stress, urgency, or mixed UI per week, a wish to be treated, and access to a smartphone or tablet. The exclusion criteria were as follows: urinary tract infection, overflow or continuous UI, indwelling urinary catheter, urogenital malignancy, pregnancy or recent childbirth (< 6 months ago), treatment for UI in the previous year, previous surgery for UI, terminal or serious illness, and cognitive impairment, psychiatric illness, or the inability to complete a questionnaire in Dutch. The present analyses used the pre-treatment data and the outcome data at 4 months for all women included in the original study.

Treatments

App-based treatment consisted of a step-by-step program for the self-management of UI, with content based on relevant Dutch GP and international guidelines.[10,12,13] Care as usual comprised referral to the participant's GP, who was then free to engage in the following routine care: discussion of treatment options, such as pelvic floor muscle training and/or bladder training; prescribing of a pessary, drugs, or absorbent products; and referral to a continence nurse, a pelvic physical therapist, or secondary care.[12]

Outcome

The outcome predicted by the model was UI severity after 4 months of treatment, which we labeled the end-UISF score. This continuous score was measured by the International Consultation on Incontinence Questionnaire, Urinary Incontinence Short Form (ICIQ-UISF),[14] a questionnaire measuring the self-reported frequency, severity, and impact on daily life of UI. Scores ranged from 0 to 21, with higher scores indicating worse incontinence. Data analysts were blinded to the treatment arm at the time of analysis.

Predictors

We identified candidate predictors based on literature search and expert opinion. PubMed was searched for predictors of conservative UI treatment and eHealth treatment (for UI and other conditions) (Supplemental Table 1).[8,9,13,16-25] We also asked independent experts in eHealth and primary care (1 pelvic floor physical therapist, 2 eHealth researchers, 1 GP with practical eHealth-experience, and 1 GP/eHealth-researcher urogynecology) to list factors they considered relevant to the success or failure of app-based and usual treatment in women with UI, as well as to comment on the factors identified by literature search. This process identified 30 candidate predictors, as summarized in Supplemental Table E2, from among which we selected 13 based on availability in our dataset and usability in clinical practice.

Based on the literature review and expert opinion, we prespecified the baseline characteristics either as potential prognostic factors or as potential modifiers. Prognostic factors predicted the outcome irrespective of treatment type, while modifiers predicted the outcome depending on the treatment received (the modifiers accounted for the difference in treatment effect in the counterfactual analysis).

Six baseline characteristics were selected as potential prognostic factors: UI severity, based on the ICIQ-UISF questionnaire (range 0–21 for low–high severity); postmenopausal state (yes or no); vaginal births (yes or no); general physical health, based on the EQ-5D-5L-VAS questionnaire (range 0–100 for low–high physical health); pelvic floor muscle function (normal, overactive, or underactive); and body mass index. Seven baseline characteristics were selected as potential modifiers, or prescriptive factors, as described by DeRubeis:[7] age (yrs); UI type (stress or urgency), duration (yrs), and impact on quality of life (ICIQ-LUTS-QoL questionnaire, range 19–76 for low–high impact); previous physical therapy (yes or no); recruitment method (through GP or media); and educational level (iMTA-MCQ-PCQ questionnaire, rated as higher or lower). Predictors were measured at baseline and educational level was assessed during follow-up.

Statistical analysis

We calculated the maximum number of parameters needed to build the model according to the guidance of Riley et al., based on a clinical prediction model with a continuous outcome and a known sample size of 262 participants.[22] Given a mean 9.9 ± 3.3-point UI severity score from our trial population and an anticipated R^2(0.6) from Nystrom et al.,[26] we calculated that a maximum of 28 parameters were needed to build the model.

Data were missing for the outcome measure and one predictor, which we accommodated by multiple imputation under the assumption of data being missing at random. We assessed the missing data mechanism by looking at patterns and predictors of missingness to substantiate assumptions of being missing at random or not at random.[27] All variables that predicted missingness of a certain variable were included in the imputation model together with all variables from the analyses.

All statistical analysis was performed using IBM SPSS for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) and R. We performed multiple imputation in R, using the MICE package, and constructed 50 imputed datasets.[28]

Development and validation

We developed a model to predict the treatment outcome based on prognostic factors and modifiers, assessed overoptimism by internal validation, and applied this as a correction. This model was used to predict two outcomes for each participant: (1) for the actual treatment the patient received, and (2) for the counterfactual treatment to which the patient was not allocated. We used these to construct and calculate the PAI, before assessing its benefits at individual and group levels.

Step 1: Development of the prediction model

We investigated multicollinearity in the non-imputed dataset by correlation matrix, which revealed that none of the candidate predictors correlated highly with another ($r > 0.8$).[29] As described by Kraemer et al., continuous predictors were mean-centered by subtracting the median and dichotomous variables were set at 0.5 and -0.5.[30] The end-UISF score was predicted by linear regression, with the potential prognostic factors entered as main effects and the potential modifiers entered as both main effects and terms representing their interactions with treatment. We used a stepwise, backward elimination strategy, excluding variables from the model based on an alpha of 0.25.[31] Predictors selected in at least 50% of the imputed datasets were included in the final model.[29] We forced treatment type and the main terms of every included interaction into the final model irrespective of their significance.[32] Model performance was assessed by R^2, goodness-of-fit, and calibration slope. The 95% confidence intervals (95%CI) are reported as appropriate.

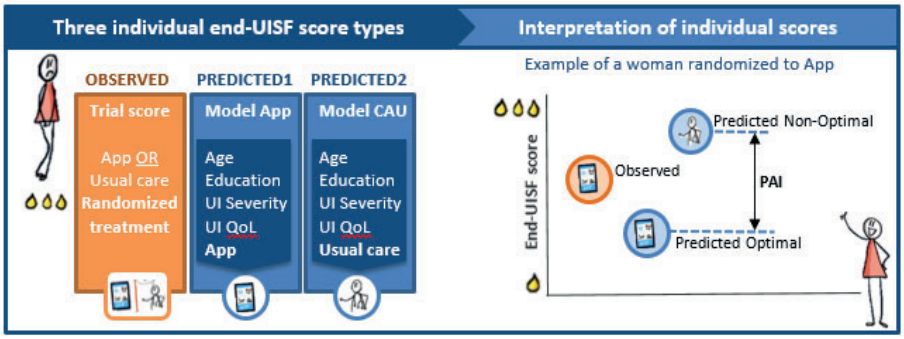
Step 2: Internal validation of the prediction model

Stability of the regression coefficients, inclusion percentages, and the mean adjusted R^2 was assessed across 500 bootstrapped samples. We examined precision with the true error (mean observed score minus mean predicted score) and the standard error. To correct for overoptimism, we applied uniform shrinkage to the final model coefficients.[29]

Step 3: Construction of the personalized advantage index

Having determined the predictors of differential response, a model can be constructed to generate treatment recommendations, making use of the PAI.[4] Given our aim to study the practical potential of this index, we focused on clinical utility over technical detail (Figure 1).[4,5]

Figure H6.1. Calculating the personal advantage index from individual predicted scores



Legend: Three individual outcome scores are possible for each patient (images, left): one observed and two predicted by the model. Optimal treatment is that with the lowest predicted outcome score (graph, right). The personalized advantage index is the difference between the optimal and non-optimal treatments.

Prediction of individual outcomes

For each patient, we predicted the end-UISF score for app-based treatment and for care as usual by completing the model twice with the patient's observed values: once with the value of app-based treatment (-0.5) and once with the value of care as usual (0.5). This predicted the end-UISF score for the treatments the patient received (factual score) and did not receive (counterfactual score). To predict individual end scores, we split the sample into five equal groups and used a linear regression model with weights based on data for four groups to predict end scores in the targeted group. This five-fold cross-validation reduced the risk of overfitting by avoiding the inclusion of an individual's own data when estimating the relevant regression coefficients.

Interpretation of individual outcomes

Three end-UISF scores were documented for each patient: (1) the observed score after receiving the randomized treatment in the trial, (2) the predicted score for app-based treatment, and (3) the predicted score for care as usual. The lowest of the two predicted scores was the optimal treatment (Figure 1).

Step 4: Assessment of the personalized advantage index

Assessment of individual benefit

For each patient, we then calculated the PAI as a measure of the benefit of one treatment over the other and assessed its magnitude (i.e., clinical relevance). The PAI was the difference between the highest and lowest predicted score. Based on a difference of 1.58 points having previously been defined as the minimum clinically important difference for the ICIQ-UISF,[26] optimal treatment with a PAI higher than this was expected to have a noticeable benefit for the patient.

Assessment of improvement at the group level

Finally, we assessed whether treatment personalization using the PAI significantly and substantially improved treatment outcomes at a group level (i.e., its utility or usefulness). Using the observed outcome scores from the trial, we compared patients who randomly received an optimal treatment with those who randomly received a non-optimal treatment. Randomization for this comparison allowed causal interpretation at the group level because we built the model on a separate selection of participants (using five-fold cross-validation) and because the predicted end-UISF scores were not tied to the randomization or treatment received.

RESULTS

Participants

We included data for 262 women who participated in the trial (Table 1). The only remarkable difference was a lower severity of UI in the app-based treatment group. At 4 months, 195 women (74.4%) had reported end-UISF scores, resulting in 67 cases of missing data for the end-UISF score and educational level. The outcome variable was missing at random and predicted by a younger age, a higher body mass index, and no prior treatment, but not by severity of incontinence.[7]

Table 1. Baseline characteristics of all participants with urinary incontinence

	Characteristic	Total (n = 262)	App treatment (n = 131)	Care as usual (n = 131)
Prognostic Factors	Severity UI at baseline*	9.9 ± 3.3	9.5 ± 3.2	10.3 ± 3.4
	Body mass index (kg/m²)*	27.8 ± 5.3	27.6 ± 5.5	28.0 ± 5.2
	Postmenopausal status, yes	123 (47.1%)	64 (49.2%)	59 (45.0%)
	Vaginal births, ≥1	216 (82.8%)	111 (85.4%)	105 (80.2%)
	Pelvic floor muscle function			
	Normal activity	84 (32.1%)	44 (33.6%)	40 (30.5%)
	Overactive	44 (16.8%)	18 (13.7%)	26 (19.8%)
	Underactive	134 (50.8%)	69 (52.7%)	65 (49.6%)
	General physical health status*	74 ± 20	73 ± 20	75 ± 21
Modifiers	Age, (years)	52.2 ± 11.6	53.2 ± 12.8	51.3 ± 10.3
	Educational level, higher	107 (52.7%)	58 (54.2%)	49 (51.0%)
	Duration of UI (years)*	7 (4-14)	7 (4–15)	8 (4–13)
	UI impact on Quality of life*	33.6 ± 8.0	33.9 ± 8.3	33.4 ± 7.8
	Type of UI			
	Stress	180 (68.7%)	87 (66.4%)	93 (71.0%)
	Urgency	82 (31.3%)	44 (33.6%)	38 (29.0%)
	Previous physical therapy for UI, yes	66 (25.3%)	31 (23.8%)	35 (26.7%)
	Recruitment type			
	General practitioner	152 (58%)	76 (58.0%)	76 (58.0%)
	Lay press or social media	110 (42%)	55 (42.0%)	55 (42.0%)

Prognostic factors predict outcomes irrespective of treatment type. Modifiers predict outcomes dependent on the treatment (modifier). Values are presented as means ± standard deviation, percentages, or medians (interquartile range). *N was lower: missing data of one baseline assessment, three baseline questionnaires, and educational level were assessed at follow-up. Abbreviations: ICIQ-UISF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form; ICIQ-LUTSqol, ICIQ lower urinary tract symptoms quality of life; UI, urinary incontinence.

Development of the prediction model

Table 2 shows the variables included in the final model. The model explained 46% of the variance in predicting the outcome measure (R^2, 0.46; 95%CI, 0.36 to 0.55)). The mean difference between observed and predicted outcomes in the original data–that is, the goodness-of-fit–was 0.015 (95%CI, -0.308 to 0.278), showing a calibration intercept at

-0.06 and a calibration slope of 1.01 (Supplemental Figure 1). A lower end-UISF score, indicating a better treatment outcome, was predicted by care as usual, lower baseline severity of UI, and lower impact of UI on quality of life. Success of app-based treatment was associated with higher age, higher impact of UI on quality of life, and higher educational level. Success of care as usual was associated with lower educational level.

Table 2: Final model predicting UI severity after 4 months (end-UISF score)

Variable	Unstandardized beta [2]	Inclusion frequency (%) 50 imputed sets	95% confidence intervals
Intercept	7.55		7.18 to 7.94
Treatment type, App (-0.5) or CAU (0.5)[1]	-0.07	100	-0.82 to 0.68
Age, yrs[1]	-0.01	2	-0.04 to 0.02
Educational level, lower (-0.5) or higher (0.5)[1]	0.01	0	-0.72 to 0.75
UI severity $_{\text{at baseline}}$	0.56	100	0.42 to 0.74
Impact of UI on quality of life[1]	0.08	100	0.02 to 0.15
Age*Treatment type	0.06	92	-0.01 to 0.12
Educational level*Treatment type	1.59	96	0.18 to 3.08
Impact on quality of life*Treatment type	0.07	58	-0.02 to 0.17

[1]Treatment type and the main interaction effects (age, educational level, impact on quality of life) were forced into the backward selection procedure irrespective of significance. [2]Uniform shrinkage was applied on beta with factor 0.98. Median centering of continuous values: Age, 51.45; UI severity, 10; Impact of UI on Quality of life, 32.
Abbreviations: CAU = care as usual, UI = urinary incontinence.

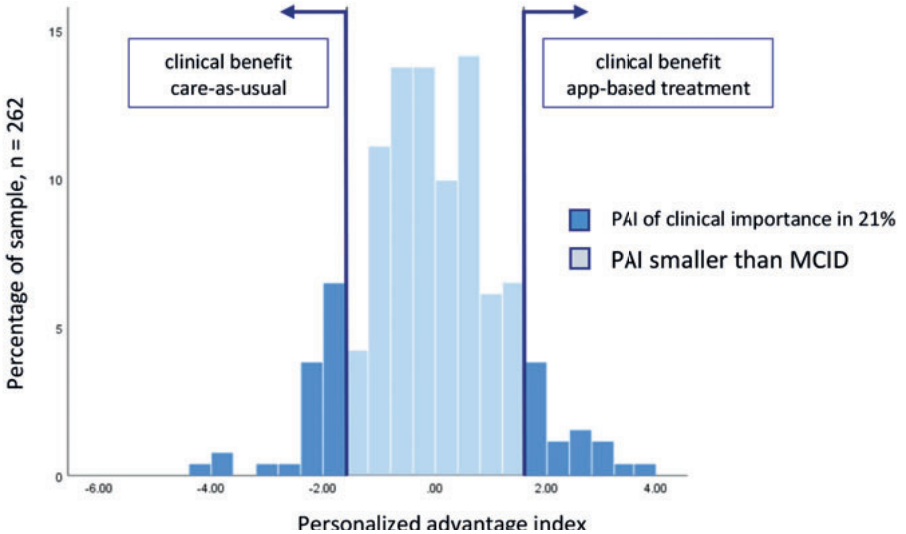
Internal validation

Regression coefficients and inclusion percentages across the bootstrapped samples were stable. The mean R^2 (% explained variance) was 0.455 (95%CI, 0.357 to 0.547) after bootstrapping (Supplemental Table 3). The uniform shrinkage factor calculated by bootstrapping was small with a factor of 0.98 (Table 2). The true error was 1.85 (values plotted in Supplemental Figure 2) and the standard error was 0.15.

Personalized advantage index

At the group level, the mean change in the unimputed observed UISF score after 4 months indicated a symptoms improvement of -2.35 ± 3.05 points. The change of symptom score varied from -15 to 6 points among patients.

Figure H6.2. Individual PAI scores and their clinical relevance



Legend: The figure shows the individual variability of treatment response above and below the minimum clinical important difference of 1.58.

Individual observed and predicted outcome scores

The observed scores showed a mean end-UISF of 7.58 ± 3.46 points (range, 0 to 18). The mean predicted optimal and non-optimal scores per patient were 7.15 ± 2.46 points (range, 0 to 13) and 8.14 ± 2.52 points (range, 2 to 16), respectively.

Individual benefit

The PAI showed a mean benefit of 0.99 ± 0.79 points for the optimal treatment over the non-optimal treatment, which ranged from 0.02 to 4.21 points at the individual level (Figure 2). This difference was clinically relevant at ≥1.58 points for 55 patients (21%).[26]

Improvement on group level

Finally, we compared the observed trial outcomes of patients receiving optimal (n = 135; 51%) and non-optimal (n = 127; 49%) treatments, which had mean scores of 7.01 ± 3.33 points and 8.20 ± 3.51 points, respectively. The PAI was considered statistically significant with a mean difference of 1.19 points (95%CI, 0.355 to 2.021).

DISCUSSION

Statement of principal findings

We illustrated a method for predicting optimal treatment and for quantifying its benefit compared with non-optimal treatment at the individual patient level when eHealth is being considered for UI management. Four baseline characteristics, namely UI severity (a prognostic factor) and age, educational level, and impact of UI on quality of life (modifiers), were identified as suitable for helping with decisions in this model. The mean advantage according to the PAI was 0.99 points, and it exceeded the threshold for clinical relevance of 1.58 in 21% of individuals. Applying the PAI to facilitate decision making also significantly improved treatment outcomes at the group level, which may be relevant when considering other measures of quality with this treatment, such as cost-effectiveness. To our knowledge, this is the first study to have translated established methods for predicting treatment outcomes from mental health and somatic disease settings[2,4,33] to an eHealth setting.

Strengths and weaknesses of the study

We developed a model for predicting the treatment option most likely to improve UI symptoms in individuals and assessed the clinical relevance of that prediction. The use of data from a pragmatic randomized controlled trial with a representative first-line population make that data well suited to developing a prediction model for personalizing treatment decisions.[2] The model is also usable because the predictors are both easily reproduced (age and answers to validated questions) and readily available in clinical practice.[1] Other strengths are the use of a patient-centered outcome measure, the selection of predictors based on literature and expert opinion, the inclusion of both prognostic factors (treatment independent) and modifiers (treatment dependent), the power of the prediction study, and the minimal overfitting of the model (shrinkage factor = 0.98).[25]

There are several important limitations that should also be considered. First, the prediction model required external validation via a sample comparing app-based treatment to care as usual; however, such a sample does not exist for UI. Internal validation only confirmed the stability of development and performance of the model. Second, the explained variance of 46% was moderate, being similar to that reported for other eHealth models for UI (range, 30% to 61.4%).[8,9] Third, the true error was 1.85 points in our sample, which is larger than the mean PAI (0.99 points) and threshold for clinical relevance (1.58 points), possibly indicating low precision for personalized predictions and probably affecting the estimation of the magnitude of an individual's advantage. Performance and precision could be increased by adding stronger predictors that interact with eHealth treatment to the model. Despite a thorough search for candidate predictors, those interacting with eHealth treatment could have been missed, especially given that literature on this topic is scarce. Finally, we could not include some variables identified by literature search and expert opinion, such as the eHealth literacy and treatment expectations of participants, because these were missing from our dataset.

Strengths and weaknesses in relation to other studies and key differences

The PAI predicted clinically relevant improvement in 60% of patients with depression for the choice between antidepressant medication and cognitive behavioral therapy.[4,5] Compared with the mental health setting,[7] clinically relevant improvement was only predicted in 21% of our cohort, possibly because there is less existing knowledge or less identifiable variation in treatment effect for UI. To date, however, we are unaware of any other studies having assessed and compared the interaction of predictors for an eHealth treatment and care as usual. We believe this type of assessment is essential to strengthen treatment-specific outcome predictions and to optimize clinical decision making for personalized medicine. Lindh et al., for example, showed that higher age predicted greater treatment success with eHealth for UI,[8] but this only considered their total sample (internet-based treatment and controls) and did not assess treatment interactions. In our study, the interaction of age with treatment type implies that a higher age may favor app-based treatment over care as usual. This new information is relevant to both researchers and clinicians because it runs counter the general expectation that eHealth is better suited to younger patients.

Possible mechanisms and explanations for findings

The predictors in our model should not be interpreted as strict causal or etiological factors for UI symptoms. The present data analysis was designed specifically to identify a set of variables that had high predictive accuracy in combination, rather than to unravel the causal factors influencing UI symptom severity at follow-up. However, the predictors that remained in the model had high a priori predictive value and are plausible causal factors.

In the developed model, increased age, educational level, and impact of UI on quality of life predicted a better treatment outcome for app-based treatment compared with care as usual. Educational level had the greatest modifying effect, with a higher level associated with benefit from app-based treatment and a lower level associated with care as usual. This is likely to reflect differences in health, eHealth literacy, and self-efficacy, but it could also reflect the app's design (e.g., there are lengthy sections of text or instructions that may be too difficult to understand) or better adaptability by a given health care professional to a patient's need for support.

Other studies indicate that lower health literacy is associated with poorer health outcomes and with difficulties utilizing eHealth effectively.[34,35] A mobile app has the potential to be tailored to specific users, such as those with low literacy, and may bridge this gap.[36] Given that the content of our app was not tailored to users with low literacy, we will develop it further to improve its availability, readability, and usability. Furthermore, we plan to add improved technological and practical support, specifically targeting users with low literacy.

Potential implications for clinicians or policymakers

Prediction modeling at a group level only allows patients and caregivers to guess how a given characteristic influences treatment outcomes at an individual level. The PAI helps to correct this by quantifying the expected outcomes and benefits of an optimal treatment over its alternative given an individual's characteristics. The results are easy to interpret and can inform decisions immediately.

Our model requires further development and validation, but in the meantime, we believe it can be of use in clinical practice. Indeed, using the tool is certainly superior to the current situation where no support is available and where its use will pose little risk to the patient if the prediction is wrong (i.e., the options are non-inferior, but its use could improve outcomes).[1] The PAI could also be implemented in clinical practice with ease, either within the app itself or on a patient information website, where the necessary prognostic factors and modifiers can be entered by users to predict the option most likely to be of benefit. This approach could be especially helpful for shared decision making and could be used to guide patients who wish to consider using a freely accessible eHealth intervention when they experience barriers seeking help from a caregiver. Currently, these patients often start to use an available app with no knowledge of what to expect.

Unanswered questions and future research

We missed important predictors by not anticipating the present analysis at the inception of our trial. Therefore, we recommend that eHealth researchers consider adding a method for personalizing treatment decisions to allow them to consider and include all relevant predictors. This is especially relevant if researchers are conducting a (pragmatic) randomized controlled trial, which otherwise provides the perfect foundation for this method.[37,2] If more eHealth researchers conducted similar research, we may see a large-scale improvement in clinical decision making, treatment outcomes, and our knowledge of the predictors that interact with eHealth treatment.

External validation of the model in the present study is needed, but this is complicated by the lack of a suitable sample. More validation samples may be available for researchers applying this method to other eHealth settings where there is a greater body of research comparing eHealth to care as usual (e.g., obesity and diabetes).[38] Finally, an impact study comparing treatment outcomes for groups with and without this decision support tool would be of interest.[1]

Conclusion

Prediction modeling can directly support decisions to personalize treatment when choosing between eHealth and care as usual. We applied this principle to an eHealth treatment for UI and, despite our model having only moderate predictive performance and still requiring external validation, we demonstrated its practical potential.

REFERENCES

1. Kummervold PE, Johnsen J-AK, Skrøvseth SO, Wynn R. Using Noninferiority Tests to Evaluate Telemedicine and E-Health Services: Systematic Review. J Med Internet Res [Internet]. 2012 [cited 2019 Feb 12];14(5):e132. Available from: http://www.jmir.org/2012/5/e132/
2. Loohuis AMM, Wessels NJ, Dekker JH, van Merode NAM, Slieker-ten Hove MC, Kollen BJ, Berger MY, van der Worp H BM. App-based treatment for urinary incontinence non-inferior to care as usual in primary care. Results of a pragmatic, randomized controlled trial. Ann Fam Med. 2020;(In press).
3. Van Diepen M, Ramspek CL, Jager KJ, Zoccali C, Dekker FW. Prediction versus aetiology: Common pitfalls and how to avoid them. Nephrol Dial Transplant. 2017;32(February):ii1–5.
4. Lindh A, Sjöström M, Stenlund H, Samuelsson E. Non-face-to-face treatment of stress urinary incontinence: predictors of success after 1 year. Int Urogynecol J. 2016; 27:1857–1865.
5. Nyström E, Asklund I, Sjöström M, Stenlund H, Samuelsson E. Treatment of stress urinary incontinence with a mobile app: factors associated with success. Int Urogynecol J. 2018; 29:1325–1333.
6. Kent DM, Steyerberg E, Van Klaveren D. Personalized evidence based medicine: Predictive approaches to heterogeneous treatment effects. BMJ. 2018;363.
7. DeRubeis RJ, Cohen ZD, Forand NR, Fournier JC, Gelfand LA, Lorenzo-Luaces L. The personalized advantage index: Translating research on prediction into individualized treatment recommendations. A demonstration. PLoS One. 2014;9(1):1–8.
8. van Bronswijk SC, DeRubeis RJ, Lemmens LHJM, Peeters FPML, Keefe JR, Cohen ZD, et al. Precision medicine for long-term depression outcomes using the Personalized Advantage Index approach: cognitive therapy or interpersonal psychotherapy? Psychol Med. 2019;(May):1–11.
9. Loohuis AM, Wessels NJ, Jellema P, Vermeulen KM, Slieker-ten Hove MC, van Gemert-Pijnen JE, et al. The impact of a mobile application-based treatment for urinary incontinence in adult women: Design of a mixed-methods randomized controlled trial in a primary care setting. Neurourol Urodyn. 2018;37:2167–76.
10. Damen-van Beek Z, Wiersma T. Practice guideline 'Urinary incontinence in women' from the Dutch College of General Practitioners. Ned Tijdschr Geneeskd. 2016;160:D674.
11. Abrams P, Andersson K-E, Apostolidis A, Birder L, Bliss D, Brubaker L, et al. 6th International Consultation on Incontinence. Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence. Neurourol Urodyn. 2018 Sep;37(7):2271–2.
12. Yoo EH, Kim YM, Kim D. Factors predicting the response to biofeedback-assisted pelvic floor muscle training for urinary incontinence. Int J Gynecol Obstet. 2011;112(3):179–81.
13. Schaffer J, Nager CW, Xiang F, Borello-France D, Bradley CS, Wu JM, et al. Predictors of success and satisfaction of nonsurgical therapy for stress urinary incontinence. Obstet Gynecol. 2012;120(1):91–7.
14. Vitacca M, Montini A, Comini L. How will telemedicine change clinical practice in chronic obstructive pulmonary disease? Ther Adv Respir Dis. 2018;12:1–19.
15. Wyman J, Allen A, Hertsgaard L, Overson E, Allen S, Hatsukami D. Effect of Smoking Cessation on Overactive Bladder Symptoms in Adults: A Pilot Study. Neurourol Urodyn. 2014;1–2.
16. Wells MJ, Jamieson K, Markham TCW, Green SM, Fader MJ. The effect of caffeinated versus decaffeinated drinks on overactive bladder: a double-blind, randomized, crossover study. J Wound Ostomy Continence Nurs. 2014; 41(4):371-378.

17. Burgio KL, Goode PS, Locher JL, Richter HE, Roth DL, Wright KC, et al. Predictors of outcome in the behavioral treatment of urinary incontinence in women. Obstet Gynecol. 2003; 102(5):940–947.

18. Cammu H, Van Nylen M, Blockeel C, Kaufman L, Amy J-J. Who Will Benefit From Pelvic Floor Muscle Training for Stress Urinary Incontinence? J Urol. 2006;191:1152–7.

19. Kim H, Yoshida H, Suzuki T. The effects of multidimensional exercise treatment on community-dwelling elderly Japanese women with stress, urge, and mixed urinary incontinence: A randomized controlled trial. Int J Nurs Stud [Internet]. 2011;48(10):1165–72. Available from: http://dx.doi.org/10.1016/j.ijnurstu.2011.02.016

20. Dumoulin C, Bourbonnais D, Morin M, Gravel D, Lemieux MC. Predictors of Success for Physiotherapy Treatment in Women With Persistent Postpartum Stress Urinary Incontinence. Arch Phys Med Rehabil [Internet]. 2010;91(7):1059–63. Available from: http://dx.doi.org/10.1016/j.apmr.2010.03.006

21. Hendriks EJM, Kessels AGH, De Vet HCW, Bernards ATM, De Bie RA. Prognostic indicators of poor short-term outcome of physiotherapy intervention in women with stress urinary incontinence. Neurourol Urodyn. 2010;29:336–343.

22. Riley RD, Ensor J, Snell KIE, Harrell FE, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. BMJ [Internet]. 2020;368(March):1–12. Available from: http://dx.doi.org/doi:10.1136/bmj.m441

23. van Buuren S. Package "mice": Multivariate Imputation by Chained Equations. CRAN Repos. 2019.

24. Steyerberg. Clinical Prediction Models: A Practical Approach to Development, Validation and Updating. Vol. 38, Kybernetes. Springer-Verlag, New York, NY; 2009.

25. Kraemer HC, Blasey CM. Centring in regression analyses: a strategy to prevent errors in statistical inference. Int J Methods Psychiatr Res. 2003;13(3):2647500.

26. Steyerberg EW. Clinical Prediction Models. Statistics for Biology and Health. 2nd edition. 2019.

27. Kleinbaum, DG, Kupper, LL, & Morgenstern H. Epidemiologic research: Principles and quantitative methods. Belmont, California: Lifetime Learning Publications; 1982.

28. Walker E. Regression Modeling Strategies. Vol. 45, Technometrics. 2003. 170–170 p.

29. Nystrom E, Sjostrom M, Stenlund H, Samuelsson E. ICIQ symptom and quality of life instruments measure clinically relevant improvements in women with stress urinary incontinence. Neurourol Urodyn. 2015;34(8):747–51.

30. Farooq V, Van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: Development and validation of SYNTAX score II. Lancet. 2013;381(9867):639–50.

31. Moons KGM, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: Application and impact of prognostic models in clinical practice. BMJ. 2009;338(7709):1487–90.

32. Asklund I, Nyström E, Sjöström M, Umefjord G, Stenlund H, Samuelsson E. Mobile app for treatment of stress urinary incontinence: A randomized controlled trial. Neurourol Urodyn. 2017;36(5):1369–76.

33. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: An updated systematic review. Ann Intern Med. 2011;155(2):97–107.

34. Jensen JD, King AJ, Davis LA, Guntzviller LM. Utilization of internet technology by low-income adults: The role of health literacy, health numeracy, and computer assistance. J Aging Health. 2010;22(6):804–26.

35. Kim H, Xie B. Health literacy in the eHealth era: A systematic review of the literature. Patient Educ Couns [Internet]. 2017;100(6):1073–82. Available from: http://dx.doi.org/10.1016/j.pec.2017.01.015

36. Liu JLY, Wyatt JC. The case for randomized controlled trials to assess the impact of clinical information systems. J Am Med Informatics Assoc. 2011;18(2):173–80.

SUPPLEMENTS

Supplemental Table 1. Summary of evidence from the literature review

Reference	Population	Study	N	Factors and effects	OR (95%CI) if available
Lifestyle					
Abrams 2018	Women with SUI, UUI, MUI, obese or overweight.	Review, 4 studies. LS: Weight loss		Weight loss of 5% -> - Reduction of UI symptoms, - Decrease pad test loss - Higher quality of life	
Wyman 2014	Men and women with UUI, smokers.	RCT. LS: Smoking	N = 57	Abstinence→ - Reduction urinary frequency	
Wells 2014	Women with UUI.	RCT. LS: Caffeine intake	N = 11	Decrease intake of caffeine→ - Reduction of frequency and urgency of UI	
Behavioral training for UI (PFMT or bladder training), *predictors of success unless stated otherwise*					
Burgio 2003	Women with SUI, UUI, MUI	3 RCTs. Behavioral training.	N = 258	Predominantly UUI (N = 198): - Lower frequency of UI episodes - Previous surgery of UI, previous treatment with medication - Lower educational level Predominantly SUI (N = 60): - No previous treatment for UI - <10 incontinence episodes per week	
Cammu 2006	Women with SUI.	Prospective cohort. Behavioral training.	N = 447	*Predictors of failure of PFMT* - ≥2 leakage episodes per day - Chronic use of psychotropic medication - Baseline positive stress test	
Kim 2011	Women with SUI, UUI, MUI	RCT. Behavioral training.	N = 127	- Compliance to treatment - BMI reduction	OR 1.13 (1.02-1.29) OR 0.78 (0.60-0.96)
Dumoulin 2010	Women with SUI	RCT. Behavioral training.	N = 57	- Baseline lower PFM passive force - Baseline greater PFM endurance	OR 0.50 (0.301-0.830) OR 1.02 (1.003-1.037)
Hendriks 2010	Women with SUI.	Prospective cohort. Behavioral training.	N = 267	*Predictors of poor outcome PFMT* - More severe stress UI - POP-Q stage >II - Poor outcome previous physiotherapy intervention - Prolonged second stage of labor - BMI>30 - High psychological distress - Poor physical health	 OR 0.09 (0.03-0.21) OR 0.10 0.01-1.05) OR 0.05 (0.01-0.32) OR 0.17 (0.05-0.56) OR 0.28 (0.08-0.94) OR 0.29 (0.11-0.89) OR 0.32 (0.11-0.87)

Reference	Population	Study	N	Factors and effects	OR (95%CI) if available
Yoo 2011	Women with SUI, UUI, MUI.	Retrospective cohort. Behavioral training	N = 86	- Change of average tonic contraction of PFM	OR 1.66 (1.015-2.721)
Schaffer 2012	Women with SUI or MUI.	RCT. Behavioral training or pessary	N = 446	- Postmenopausal status - Higher educational level - No previous UI surgery	OR 2.52 (1.29- 4.95) OR 1.61 (1.01-2.55) OR 3.15 (1.04-9.53)
mHealth					
Lindh 2016	Women with SUI.	RCT. Behavioral training (PFMT) via internet or brochure	N = 169	- Higher age - Regular performance of PFMT after 1 year	OR 1.06 (1.02-1.10) OR2.32 (1.04-5.20)
Nystrom 2017	Women with SUI.	Cohort from RCT. Behavioral training (PFMT) via app.	N = 61	- Higher expectations of treatment effect - Weight control (per kg gained) - Self-rated improvement of PFM strength	OR 11.38 (2.02-64.19) OR 0.44 (0.24-0.79) OR 35.54 (4.96-254.61)
Vitacca 2015	COPD patients	Review of telemonitoring outcomes from RCTs	46 RCTs	- Higher age - Worse severity of disease and more frequent exacerbations - Limited community support - Home care not widely available	Not applicable

Behavioral training = Pelvic Floor Muscle Training and/or bladder training. Abbreviations: SUI = Stress urinary incontinence, UUI = Urgency urinary incontinence, MUI = Mixed urinary incontinence, LS = Lifestyle change.

Supplemental Table 2. Complete list of candidate predictors and selected predictors for successful UI treatment by care-as-usual and eHealth

Candidate predictors	Related to conservative management and/or eHealth	Literature and/or expert opinion	Available in data	Selected *with expected interaction treatment
Age	Both	Both	Yes	Yes*
Educational level	Conservative management	Literature	Yes	Yes*
Smoking	Conservative management	Literature	-	-
Caffeine consumption	Conservative management	Literature	Yes	-
Body Mass Index (BMI)	Conservative management	Literature	Yes	Yes
Limited care available/ lower mobility of patient	eHealth	Literature	Yes	-
Poor physical health status	Conservative management	Literature	Yes	Yes
Self-efficacy	eHealth	Expert	-	-
Being a caregiver to a sick spouse or parent	eHealth	Expert	Yes	-
Having a job	eHealth	Expert	Yes	-
Social support	eHealth	Expert	-	-
UI: severity	Both	Literature	Yes	Yes
UI: frequency	Conservative management	Literature	Yes	-
UI: type	Conservative management	Both	Yes	Yes*
UI: duration of symptoms	Conservative management	Expert	Yes	Yes*
UI impact on quality of life	Conservative management	Expert	Yes	Yes*
Menopausal state	Conservative management	Literature	Yes	Yes
Vaginal births	Conservative management	Literature	Yes	Yes
Pelvic floor muscle function at baseline	Conservative management	Literature	Yes	Yes
Prolapse according to POPQ system	Conservative management	Literature	Yes	-
Sense of pelvic floor muscles	Conservative management	Expert	-	-
Expectations of treatment	eHealth	Literature	-	-
Adherence to treatment	Both	Both	-	-
Duration of treatment	Conservative management	Literature	-	-
Previous treatment	Conservative management	Literature	Yes	Yes*
Previous experience with smartphone or tablet (digital) usage	eHealth	Expert	-	-
eHealth literacy	eHealth	Expert	-	-
Follow-up yes or no	eHealth	Expert	Yes	-
Recruitment method (GP or (social) media)	eHealth	Expert	Yes	Yes*

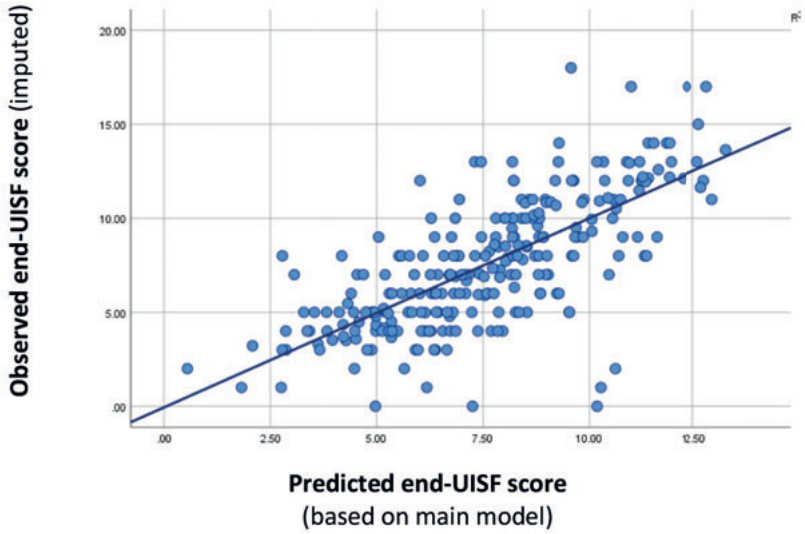
Abbreviations: UI = urinary incontinence

Supplemental Table 3. Inclusion frequencies of the regression coefficients from 500 bootstrap samples

Variable	Bootstrap	
	inclusion frequency (%)	95% confidence intervals
Intercept		7.21 to 7.89
Treatment type, App (-0.5) or CAU (0.5)*	100	-0.69 to 0.51
Age, yrs*	25	-0.03 to 0.02
Educational level, lower (-0.5) or higher (0.5)*	23	-0.52 to 0.763
UI Severity $_{\text{at baseline}}$	100	0.43 to 0.74
Impact of UI on Quality of Life *	96	0.03 to 0.14
Age*Treatment type	80	0.01 to 0.10
Educational level*Treatment type	94	0.44 to 2.99
Impact on Quality of life*Treatment type	62	0.01 to 0.14

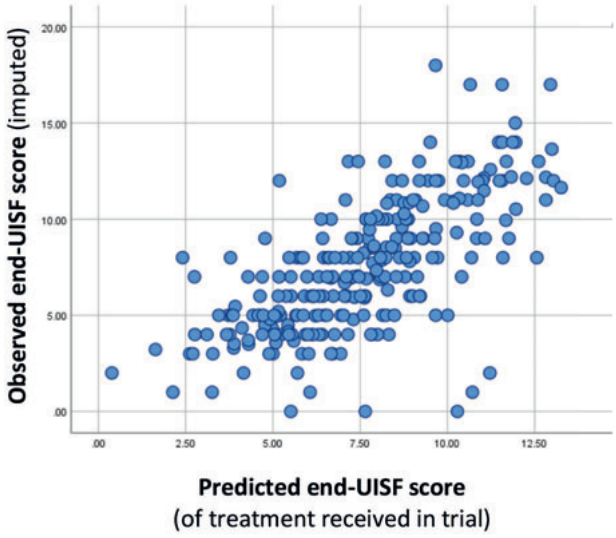
*Treatment type and the main effects of the interactions (Age, Educational level, Impact on quality of life) were fixed in the backward selection procedure. CAU = care-as-usual, UI = urinary incontinence

Supplemental Figure 1. Calibration slope of observed versus predicted end-UISF scores (prediction based on the main model).



The calibration intercept is at -0.06 and the calibration slope is 1.01.

Supplemental Figure 2. Scatterplot of observed versus predicted end-UISF scores (predicted score of treatment received in the trial



CHAPTER 7

Barriers And Facilitators Associated With App-Based Treatment For Female Urinary Incontinence: A Mixed-Methods Evaluation

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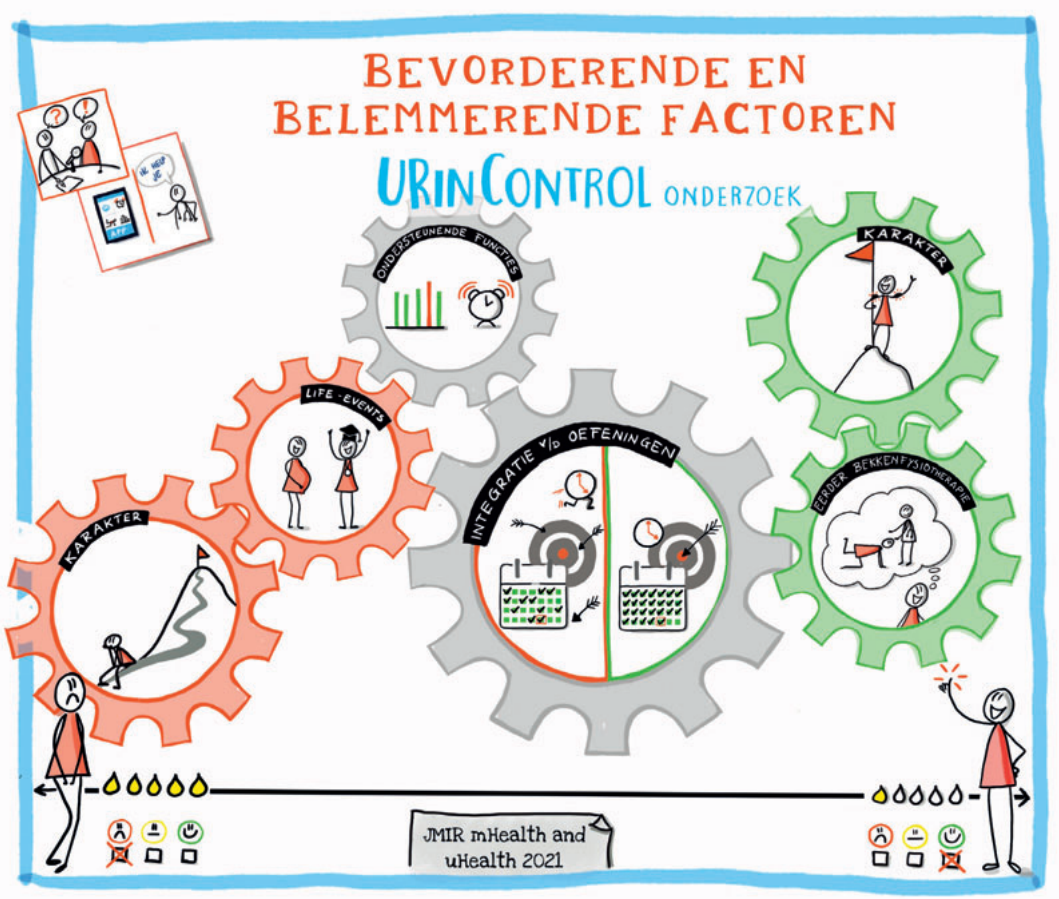
BEVORDERENDE EN
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KARAKTER
LIFE-EVENTS
INTEGRATIE V/D OEFENINGEN
KARAKTER
TERUGVERWIJZING BEKKENFYSIOTHERAPIE
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ABSTRACT

Background: App-based treatment for urinary incontinence is a proven effective and cost-effective alternative to care-as-usual, but successful implementation requires that we identify and address the barriers and facilitators associated with app use.

Aim: To explore the factors influencing the success or failure of app-based treatment for urinary incontinence.

Design and Setting: We used a sequential explanatory mixed-methods design to connect the results of a randomized controlled trial (RCT) with data from semi-structured interviews.

Method: A previous RCT had shown the non-inferiority of app-based treatment compared with care-as-usual for urinary incontinence over 4 months. Participants who reported success or failure with app-based treatment, as measured by the change in ICIQ-UI-SF symptom score, were selected for telephone interview by purposive sampling (n = 17). The qualitative results from these interviews were then compared between the success and failure group to explore factors that were positively or negatively associated with the quantitative effect of app-based treatment. These factors were then interpreted as barriers to and facilitators of successful app-based treatment.

Results: Four interrelated themes were identified as affecting the app based treatment effect: "Adherence," "Personal Factors," "App Factors," and "Awareness." Adherence-related factors directly influenced treatment effect. In turn, adherence was also influenced by the other three themes. Additionally, awareness was influenced by the treatment effect. From these themes, several factors were identified that acted as barriers (e.g., time investment), facilitators (e.g., prior pelvic floor muscle therapy), or both (e.g., personality traits and increased awareness of symptoms).

Conclusion: The insights obtained in this study into the barriers and facilitators associated with app-based treatment for UI could lead to improved implementation and increased treatment effectiveness by targeting women most likely to benefit and through further development of the app.

INTRODUCTION

App-based treatment for urinary incontinence can be an effective and cost-effective alternative to care-as-usual.[1-3] Although implementation must now proceed for us to realize these benefits for patients and caregivers, success will require that we identify and address the barriers and facilitators associated with this treatment modality.[4] Previous qualitative studies of women suffering from urinary incontinence have identified factors that could affect app- or internet-based treatment for urinary incontinence by exploring their expectations and experiences.[5-8] Women expected that internet-based treatment would be more accessible, more flexible, and improve treatment adherence, but they expressed concern about the lack of contact with a caregiver.[5] Three studies have also described the experiences of women using internet- or app-based treatment for urinary incontinence over periods of 6 weeks to 3 months.[6-8] Women commented on several positive and negative effects: acknowledgment and flexibility [6], support via reminders, insecurity of the treatment result[7], and increased awareness of symptoms.[8] However, these experiences of internet- or app-based treatment for urinary incontinence were never assessed in relation to quantitative treatment success or failure. It is important to explore if a relation exists between the factors identified in qualitative research and the actual success or failure of the intervention.[9] This could reveal strategies for tailoring the app, increasing its effects, or targeting women most likely to benefit.

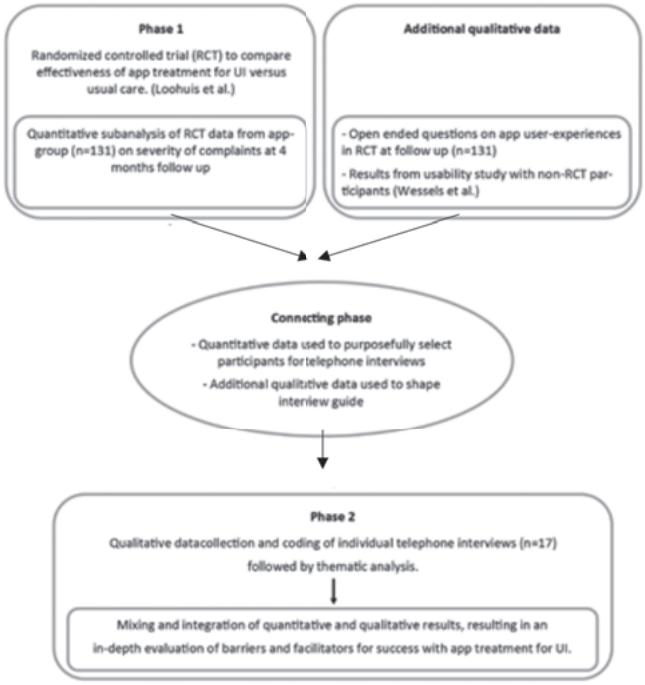
In this study, we aimed to explore the factors influencing app-based treatment for urinary incontinence and to identify which barriers or facilitators are associated with treatment success or failure.

METHODS

Study design

We conducted a mixed-methods study with a sequential explanatory design that built on a previously reported quantitative randomized controlled trial (RCT) by integrating the results of a qualitative analysis of interviews. The qualitative phase reported in this manuscript follows on from a quantitative phase that was reported elsewhere [3,10] (Multimedia Appendix 1 summarizes the design) and links both phases in a connecting phase (Figure 1). The original RCT showed the non-inferiority of app-based treatment for urinary incontinence (containing a step-by-step self-management program based on Dutch general practitioner (GP) and international guidelines[11,12]) compared with care-as-usual after 4 months[3] and for the current study we used the quantitative outcomes of the URinControl RCT to select participants for telephone interview by purposive sampling. The qualitative results from the interviews were expected to refine and explain the quantitative results by exploring participants' views in more depth.[9,13,14]

Figure H7.1 Description of sequential explanatory mixed methods study to explore barriers and facilitators for success with app treatment for UI



Participants

We used purposive sampling to select women for interview from the app-based treatment group according to the change in symptom severity measured by the International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form (ICIQ-UI-SF) at 4 months.[15] We ranked the change in ICIQ-UI-SF score from the largest increase to the largest decrease in symptoms and invited participants by working inwards from these extremes. In this way, we created two groups: a treatment success group and a treatment failure group. We approached women who had completed the 12-month follow-up requirement to avoid influencing the ongoing RCT. Women were invited by telephone, after which an appointment was made for a telephone interview.

Data collection

The semi-structured interview guide contained several broad themes to ensure that all relevant topics were covered in the interviews. These were selected based on a literature review and the results of a study into the experiences of URinControl app users not included in the RCT.[8] We also reviewed the answers to open-ended questions regarding the experiences of all users in the app group to help further shape the interview guide (see *Connecting Stage* in Figure 1).

A female medical master's student (LA) who had no prior relationship with the participants conducted telephone interviews in April and May 2019. She was experienced in performing in-person interviews and prepared for the current task by conducting an extensive literature review on this subject. Additionally, we held a pilot interview and regular peer debriefings to evaluate the quality of the interviews. The interviewer encouraged participants to elaborate on their experiences and asked them to raise any subject they felt relevant but that had not yet been covered. Interviews where audio recorded and transcribed verbatim.

Data analysis

Qualitative analysis was driven by an inductive approach, allowing new patterns and categories to emerge from the raw data. Interview transcripts were coded separately by two researchers (NW, LA) using Atlas.ti (version 8.4), and the codes and emerging categories were compared and checked for consensus. Additionally, we regularly discussed broader themes emerging from the categories within the research group and compared with the raw data to ensure that the themes covered all aspects. Interviews were conducted until saturation (no new categories emerged in three consecutive interviews). Analysis then proceeded in two stages. First, we focused on the coded data of all interviewed participants and discussed the relationships between the main themes. Second, we integrated the quantitative and qualitative data by comparing and contrasting the experiences between the success and failure groups, describing the between-group differences in subthemes and the relations between main themes. Additionally, between-group differences in subthemes were checked by frequency counts. Multimedia Appendix 2 and 3 provide a more detailed description of the qualitative analysis and the coding tree.

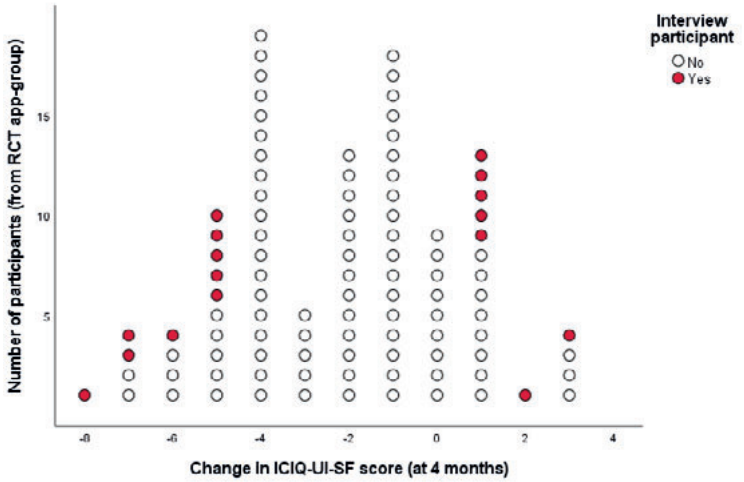
The descriptive analysis of participant characteristics was conducted with IBM SPSS, Version 26 (IBM Corp., Armonk, NY, USA). The Research Ethics Committee of University Medical Center Groningen approved the study (no. M17.207954), and all participants provided written informed consent. Reporting was in accordance with the Consolidated Criteria for Reporting Qualitative Research. [16]

RESULTS

Participant selection and characteristics

The change of urinary incontinence severity measured with the ICIQ-UI-SF in the 102 women with complete follow-up at 4 months ranged from -8 to +3 points (mean 2.2, SD 2.56) (Figure 2). Three women had not completed 12 months of follow-up, so were not invited, and five women declined the invitation to participate. Data saturation was reached after the 17th interview.

Figure H7. 2. Overview of the interview participants (n = 17) with respect to the total RCT app group (n = 102)



ICIQ-UI-SF change scores: negative scores indicate symptom improvement ("success") and positive scores indicate symptoms increasing ("failure").

ICIQ-UI-SF change scores: negative scores indicate symptom improvement ("success") and positive scores indicate symptoms increasing ("failure"). The interviewed women were aged 35–78 years and had suffered from urinary incontinence for between 3 months and 20 years (Table 1). Overall, 9 and 8 women experienced treatment "success" and "failure," respectively (Figure 2): the change in ICIQ-UI-SF score for women from the success group ranged from -8 to -5 points (median, -5.5); for the failure group, it ranged from 1 to 3 (median, 1.5). Patients from the success group seemed to have worse UI-specific measures and higher age at baseline. Educational level and relevant experiences seemed comparable between groups. None of the patients from the failure group experienced a worsening of symptoms (Patient Global Impression of Improvement (PGI-I) < 4).

Table 1. Characteristics of the interview participants*

	Participants		UI Outcomes		UI at baseline				Relevant experience	
#	Age, yrs	Level of educationa	Severityb, change	PGI-Ic	Severity, score	Impactd, score	Type	Duration, yrs	Previous PFMT	Smartphone /tablete, yrs
Treatment success										
01	65	Higher	-6	6	10	33	Stress	4	No	8
02	67	Higher	-8	6	16	59	Urge	5	No	2
03	54	Lower	-7	7	12	42	Stress	20	Yes	2
04	61	Lower	-5	6	10	37	Stress	20	Yes	5
05	46	Higher	-5	6	7	32	Stress	2	No	8
06	48	Higher	-7	5	13	36	Stress	6	No	15
07	71	Higher	-5	5	14	51	Urge	15	No	8
08	78	Lower	-5	6	10	37	Stress	20	Yes	1
09	44	Lower	-5	5	11	32	Urge	15	No	-
Treatment failure										
10	54	Lower	2	6	6	32	Stress	5	No	5
11	65	Lower	3	4	5	23	Stress	10	No	6
12	48	Lower	1	6	12	51	Stress	12	Yes	10
13	48	Higher	1	5	4	25	Urge	16	No	10
14	43	Higher	1	4	5	27	Urge	0.25	No	3
15	63	Higher	1	4	4	32	Urge	3	No	7
16	42	Higher	1	6	7	26	Stress	0.42	No	6
17	35	Lower	1	5	9	27	Urge	20	Yes	-

*Women using app-based treatment purposefully sampled based on change of UI Severity (ICIQ-UI-SF score) after 4 months

All measures were self-reported and recorded at baseline, except for the ICIQ-UI-SF change score and the PGI-I which were recorded at 4 months follow-up.

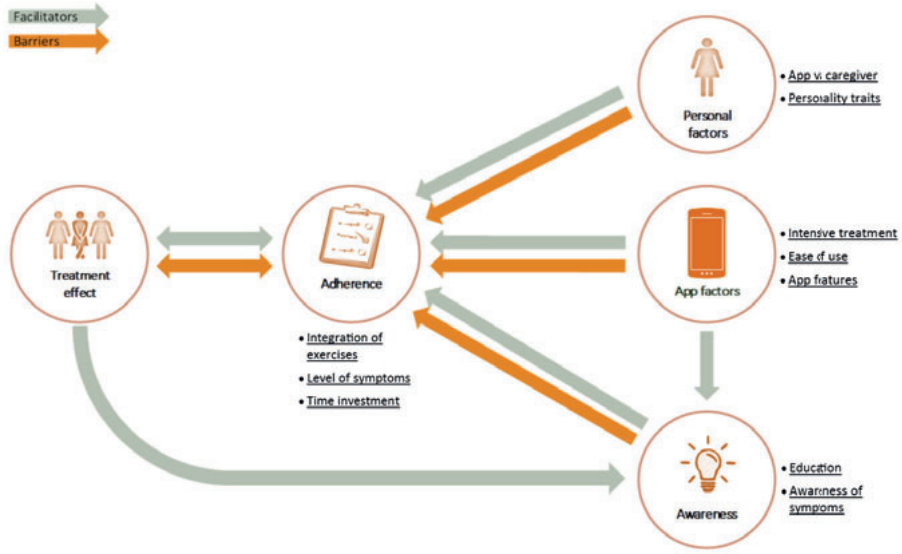
Abbreviations: UI, urinary incontinence; PFMT, Pelvic floor muscle therapy.

[a] Lower: primary or secondary education. Higher: tertiary education or higher. [b] Severity based on ICIQ-UI SF, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form, range 0-21, higher score is worse incontinence; [c] PGI-I, Patient Global Impression of Improvement, Likert scale ranging from 0 (very much worse) to 7 (very much better), with 4 reflecting no change. [d] Impact based on ICIQ-LUTSqol, ICIQ lower urinary tract symptoms quality of life, range 19-67, higher score reflects larger impact of UI on QoL. [e] Years in possession of device

Semi-structured interviews

We identified "Adherence," "Personal Factors," "App Factors," and "Awareness" as the main themes related to overall treatment effect. Discussion of the relationships between the themes resulted in a cross-thematic network (Figure 3). Factors in the Adherence theme directly influenced app-based treatment effects as a barrier and facilitator. Adherence was further influenced by factors in the Personal Factors, App Factors, and Awareness themes (barriers and facilitators). Finally, Awareness was facilitated by the treatment effect and by App Factors.

Figure H7.3. Cross-thematic network of interrelated themes resulting from the qualitative analysis of telephone interviews (n = 17). Subthemes show the barriers or facilitators for successful app treatment



There were no differences between the success and failure groups in the main themes or relationship directions, but there were differences between those groups in the subthemes and in the strength of the relationships between the main themes. The frequency counts for quotes showed between-group differences in subthemes with clear patterns that matched those found in the interviews (Table 2).

Table 2: Themes and subthemes by treatment success and failure

The experience of app treatment for urinary incontinence		GROUPS	
Theme	**Subtheme**	**Success Group**	**Failure Group**
Personal factors	App vs caregiver		
	- Prior Pelvic floor muscle therapy	3	
	- Being independent of care provider	3	4
	- Insecure about correctly performing exercises	2	1
	- Lowering shame barriers	2	
	Personality traits - Positive: e.g. go-getter disciplined	2	
	- Negative: e.g. slacking-off	2	4
App factors	Intensive treatment	3	2
	Ease of use		
	- Devices • Tablet	3	3
	• Smartphone	6	6
	- Complex user interface	3	2
	- Lessons (exercise levels) • Useful	7	5
	• Not useful	1	1
	App features		
	- Reminders • Useful	4	3
	• Not useful	6	2
	• Timing inconvenient	3	4
	- Graphs • Useful	3	1
	• Not useful	5	7
Awareness	Education	5	3
	Awareness of symptoms		
	- Positive	9	5
	- Negative		2
Adherence	Integration of exercises	4	6
	Level of symptoms		
	- Recurrence of symptoms (positive)	5	1
	- Improvement of symptoms (positive)	1	
	Time investment (negative)		2
	- Personal circumstances (negative)	3	5

Numbers are representative of how many participants mentioned the subtheme throughout the interviews.

Adherence

The Adherence theme covered factors affecting the level to which participants felt they adhered to treatment advice (i.e., app usage and performing exercises). Women in both groups felt that their adherence was directly related to the treatment effect, and it was evident that increasing and decreasing symptoms each affected their motivation to adhere to treatment. Several subthemes emerged.

Integration of exercises

The intensive treatment and frequent reminders provided by the app helped women to perform exercises at set times. This enabled them to establish an exercise routines that suited their schedules which contributed to the overall treatment effect women experienced. Women in the failure group tended to describe less strict exercise regimes than women in the success group.

"After a while you'll get into a certain rhythm. I did it on my way to work [...] those are the moments you remember, so you get a regularity to it. That is pretty nice." (P6, Success)

"Or when I'm in the car, I have nothing to do, and I'm bored; during a long drive, for example. They are the kind of exercises you can do everywhere with no-one taking notice." (P10, Failure)

Level of symptoms

Women in both groups mentioned that symptom severity influenced adherence, both positively and negatively. One woman in the failure group stated that her low symptom level meant that she lacked the motivation to persevere with the exercises, resulting in minimal treatment effect. Women in the success group more often stated that both symptom improvement and symptom recurrence after a period of less adherence motivated them to start again, hereby enhancing their training results.

"No, I think that my complaints need to be more severe for that [increased adherence]. Now I just think 'I'll use a pantyliner and I'll be done with it.'" (P15, failure)

"[...] That's why I keep doing it. Because I stopped for about three weeks, because I had surgery on my foot and was hospitalized for it. But after that I could notice that I hadn't done it. (P8, Success)

Time investment

Some women in the failure group felt that the treatment program was much more time consuming than expected, which markedly decreased their adherence and limited their treatment effect. A lack of time due to personal circumstances, such as illness, family

reasons, or life events also negatively influenced adherence in both groups, but this was mentioned more by women in the failure group.

Personal factors

This theme covers personality traits and attitudes toward app-based treatment in comparison with treatment by a care provider.

App versus caregiver

Women in both groups valued the concept of 24-hour treatment availability and liked being independent of a care provider. This enabled them to be in control of their own treatment and to combine it with their busy and irregular lifestyles, which made it easier for them to adhere to the treatment.

"Great [opinion about being randomized in app group], because in all honesty, I wasn't looking forward to it at all. I thought, then I'll have to go a GP and make another appointment again. But with an app, you are the one in control, which is much easier." (P15, Failure)

A few women mentioned they occasionally wondered if they performed the exercises correctly, and although none had consulted a care provider, they stated that they might do so in the future. For some women in the success group, preference for the app arose from having experienced insufficient results from prior physical therapy for incontinence. Additionally, one woman stated that she preferred the app because she felt a major barrier when talking about her symptoms.

"I thought it would be very convenient to try the app, because this [urinary incontinence [] is not something I would easily consult my GP for. [...] It's just not something people talk about." (P1, Success)

Personality traits

Personal characteristics were frequently mentioned as barriers or facilitators of success. Women in the success group mainly declared it was a matter of "just doing it" and being a bit of a go-getter to continue with the exercises on a regular basis. Conversely, women in the failure group tended to focus on negative traits and described to know themselves as sloppy and not being able to persevere, which negatively impacted their adherence.

"It's just a matter of carry-on, and you'll start getting results." (P3, Success)

"That is the same as going to the dentist and thinking, maybe I should brush my teeth thoroughly for a change [laughs]. [...] It's not so much the app having to change, I think it [low adherence] is something engrained in humans." (P12, Failure)

App factors

Subthemes related to App Factors (i.e., experiences with different features) included the "intensity and extensiveness of treatment," "ease of use of the app," and "features within the app."

Intensive treatment

Women in both groups appreciated the intensive and extensive treatment program offered by the app, indicating that they felt this was something a caregiver could not provide.

"[...] I think you are more dedicated to it, especially at the start. When you go to the physical therapist, you get some exercises, You go home, and you do those. But with the app, you just do it every day." (P4, Success)

Ease of use

Most women installed the app on their smart phone because this device was always at hand, which made it easier to adhere to the intensive treatment. Others preferred a tablet because of the larger display or because they did not possess a smart phone or know how to operate one. Most women in both groups found the app easy to use and appreciated the clear instruction provided in the lessons. However, a few women stated that the app's user interface was overly complex, taking too long to identify where to start and to get an overview of the content. This negatively impacted their motivation to use the app.

App features

Most women tried the app's reminder function, but it yielded mixed feelings regarding the effect on their treatment adherence. Despite being able to set three reminders per day, many women in each group found the timings inconvenient or did not want to receive a reminder when they were with other people. Also, some women were unaware that the app provided this function. Overall, despite many women appreciating the inclusion of a reminder function, a slightly larger cohort (mainly from the success group) stated that they ultimately stopped using this feature.

"No, I felt those [reminders] were actually only annoying because I already had my own vision of when I was generally going to practice." (P12, Failure)

"I was planning on doing them only when I was by myself. I did not want to receive a reminder when I was out somewhere." (P1, Success)

Some women stated that the graphs provided insights about progression and made them more aware of their symptoms, but only a few participants used and appreciated this function. When used, the function did give a sense of being on the right path and

encouraged perseverance. One participant from each group stated they thought it would have been more motivational to have a graphical display showing symptom changes. However, many women, mostly from the failure group, found that the graphs were difficult to interpret or that they added little. One woman declared that she found looking at the graphs to be too confrontational.

"I would leave that out; when you've practiced and all the statistics. If you skipped that for a day, you'll start feeling guilty." (P16, Failure)

Awareness

There was increased awareness in several domains. Awareness increased concerning knowledge of the disease (education) and awareness of symptoms. This increased awareness could act as either a facilitator of, or a barrier to, adherence. Furthermore, awareness increased directly with both app factors (reminders) and treatment effects (symptom improvement or recurrence).

Education

Women in both groups found the information provided by the app useful. Many had thought urinary incontinence was a part of life they had to accept. Knowledge about the possible effect of conservative therapies enhanced their motivation to carry on with the exercise program. Others stated that they felt less alone dealing with urinary incontinence knowing that other women experienced the same symptoms.

Awareness of symptoms

The intensive treatment resulted in increased awareness of the impact of symptoms and of the coping strategies used. In general, women in both groups appreciated this aspect. In the failure group, women stated that they liked knowing what to do to improve their symptoms. In the success group, women tended to report putting this knowledge into action, stating several key benefits: that they felt more confidence in their treatment; that it helped them to make lifestyle changes; and that it helped to lessen the sense of taboo when talking with other women about symptoms.

"Well, I certainly know what to do now to get results. I know that I have to do it for months, then it will work. That I understand." (P11, Failure)

"It gave me some reassurance in the sense of, 'that should be doable.' And that already made it easier to postpone toilet visits." (P7, Success)

Conversely, a few women in the failure group stated that they did not like the increased focus on themselves and their problems, which made them less motivated to use the app. One even wondered if this had led to her symptoms increasing.

DISCUSSION

Summary

Our findings provide new insights into the barriers and facilitators associated with successful app-based treatment for urinary incontinence, principally showing that the effect of each explored factor results from whether there is treatment success or failure. Moreover, the views of patients concerning adherence to app usage and to performing the recommended exercises were key. Comparison between the success and failure group revealed several factors that facilitated treatment success, namely strict integration of exercises, previous experience of face-to-face PFMT with insufficient effect, and being a so-called "go-getter"; by contrast, we identified the barriers as being unrealistic expectations of time investment, interfering personal circumstances, and being unable to persevere. Of note, however, the graphs and reminder functions did not have the expected facilitating effect, and indeed, sometimes acted as a barrier. It was interesting that the general increased awareness after treatment and the awareness of symptom change positively and negatively affected adherence and treatment effectiveness. We believe these facilitators and barriers can be used to improve outcomes with app-based therapy.

Strengths and limitations

This is the first study using a sequential explanatory design to assess the facilitators of, and barriers to, app-based treatment for urinary incontinence. We consider the mixing and integration of qualitative and quantitative data throughout the study to be an important strength, helping to improve the quality of our conclusions.[10] This approach produces a whole that is greater than the sum of the individual qualitative and quantitative parts.[17] We also selected high- and low-performing cases to explore the contrast between treatment success and failure[9], which enabled us to identify facilitators and barriers associated with the desired treatment effect. Other strengths of our design were the use of previously collected qualitative data to build the interview guide, the re-evaluation of themes within each outcome group, and the use of quote frequency counts.

Despite these notable strengths, however, there were some important limitations. For example, there was no member check due to logistic difficulties, and eight women were unavailable for interview, potentially affecting the identified themes. Additionally, it should be noted that the exploratory nature of this type of (qualitative) research allows for hypothesis-generation, not hypothesis testing. Therefore, when interpreting the results, one should keep in mind that this research is not able and does not seek, to predict treatment effect. This research rather explores the factors influencing treatment from a qualitative participant's perspective and relates these to the quantitative treatment effects.

Participant selection for the interviews was based on follow-up outcomes at 4 months, which we anticipated would reflect the optimum treatment effect. However, interviews were postponed until after the 12-month follow-up to limit interference with the trial. Although this extension allowed us to explore facilitators and barriers in both the short- and long-term, it could have introduced recall bias in the women's experiences and perception of factors influencing effectiveness in the first 4 months.

There was also some inconsistency with the concepts of failure and success. Among the women with a deterioration in urinary incontinence severity on the ICIQ-UI-SF at 4 months, none perceived a worsening on the PGI-I at that time and none reported treatment "failure" in the interviews after 12 months. Recall bias could explain the inconsistency between the ICIQ-UI-SF at 4 months and the interview after 12 months, but not the difference between the PGI-I and the ICIQ-UI-SF, both of which were measured at 4 months. Thus, it may be that these differences indicate that the perception of improvement reflects not only the change in urinary incontinence symptoms but also better coping strategies or decreased shame due to increased knowledge.

Comparison with existing literature

Previous studies have included women with no experience of eHealth for urinary incontinence, using eHealth for urinary incontinence for 6 weeks to 3 months, and with no case-selection based on treatment effect.[5-8] In this study, we explored the experiences of women using the app for 12 months who had showed a clear worsening or improvement of symptoms. Although we identified similar main themes, we could also further explore the relationship between those themes and the treatment effect. Consistent with existing research, women from both of our study groups expressed positive views about the availability, flexibility, privacy, and education provided by eHealth for urinary incontinence.[5-8]

Insecurity about exercise performance. Women's feelings in our study were mixed with regards to insecurities about the correct performance of exercises. Firet et al. described that women had experienced their pelvic floor muscles to be difficult to contract correctly during face-to-face PFMT.[5] Elsewhere, Asklund et al. reported that a lack of reassurance created insecurity when women thought contractions were "good enough," but were left wondering if personal instruction could lead to improvements.[7] In our study, women expressed these insecurities in both the success and failure groups, but despite being instructed to consult a health care professional if they needed, none sought further advice. This suggests that the presence of insecurity about treatment is not a differentiating factor for treatment success or failure. Instead, treatment failure in women with insecurities may have reflected other barriers (e.g., not being able to persevere or having interfering personal circumstances) or different coping strategies, with insecurities and doubts keeping them from consulting a caregiver.

Awareness of urinary incontinence symptoms and treatment options acted as both a facilitator and a barrier for women in our study, whereas in other studies, increased awareness has mainly been described positively.[6,7]

Increased awareness - positive effects. Positive effects found in our study were an increased awareness of symptoms and of the treatment options, which lessened the sense of taboo around the topic and encouraged women to change their lifestyles. Additionally we confirmed that awareness of symptom recurrence after a period of less adherence stimulated motivation, as Asklund et al. also described.[7]

Increased awareness - negative effects. Negative effects were related to a negative focus on symptoms and a decrease of adherence to treatment. The increased negative focus on symptoms in some women acted as a barrier as it kept them from continuing app usage, which was also reported by Wessels et al.[8] Also, for some women, awareness of symptom improvement during treatment led to decreased motivation to adherence to the treatment. *App features.* Additionally, it was notable that reminders did not facilitate treatment success and that the graph function was deemed too confrontational or unhelpful, contrasting with our expectation that these would positively affect motivation and adherence.[7,8] This may be related to the long 12-month follow-up period. For example, the facilitating effect of reminders may have been small or only present early on, potentially being lost due to recall bias. The sense that the graphs were confrontational may have appeared over time in response to a lack of treatment effect, but this may also have resulted because the graphs only monitored lack of adherence, rather than progress or change in urinary incontinence symptoms. Asklund et al. showed the same statistics in their graph usage but did not report this confrontational effect.[7]

Implications for research and/or practice

The findings of our study can be used to increase the effect of app-based treatment by targeting women who are most likely to benefit and by showing how we can better tailor app-based treatments. When the app is made available to the wider public, it will be important to inform potential users about the various factors that can influence the treatment effect. When care providers discuss the use of app-based treatment for a patient with urinary incontinence, our findings indicate that it is crucial they consider personality traits (e.g., highly self-motivated), expectations of time investment, and previous experiences with regular PFMT. We can tailor the app-based treatment to increase the treatment effect by modifying the graph and reminder functions. Graphs could be an optional tool that are simplified to emphasize urinary incontinence symptom progression rather than lack of adherence. To reduce the perceived intrusion of the reminder function, this could be revised to a "daily to-do list" with no pre-set times. Finally, future research could be focused on further examining the characteristics of women in whom app-based treatment failed, because this might be a distinct group with similar personality traits.

This knowledge could help health care professionals provide the necessary support for patients to achieve treatment success.

In conclusion, this study shows that the effect of app-based treatment for urinary incontinence is mainly influenced by adherence, which in turn, is affected by personal factors, app-based factors, and awareness. However, it was notable that the identified factors could function as both facilitators and barriers depending on the user and the interaction with other factors. Insight into these facilitators and barriers can be used to increase the treatment effect of app-based treatment for urinary incontinence by ensuring that we target women most likely to benefit. Introducing some minor changes to the graph and reminder functions could improve the usability of our app.

REFERENCES

1. Asklund I, Nyström E, Sjöström M, et al. Mobile app for treatment of stress urinary incontinence: A randomized controlled trial. Neurourol Urodyn. 2017;36(5):1369–76.
2. Sjöström M, Lindholm L, Samuelsson E. Mobile app for treatment of stress urinary incontinence: A cost-effectiveness analysis. J Med Internet Res. 2017;
3. Loohuis AMM, Wessels NJ, Dekker JH, et al. App-based treatment for urinary incontinence non-inferior to care as usual in primary care. Results of a pragmatic, randomized controlled trial. Ann Fam Med. 2020; (In press).
4. Schreiweis B, Pobiruchin M, Strotbaum V, et al. Barriers and facilitators to the implementation of eHealth services: Systematic literature analysis. J Med Internet Res. 2019;21(11):e14197.
5. Firet L, Teunissen D, Verhoeks C, et al. Expectations regarding eHealth among women with stress urinary incontinence. Int Urogynecol J. 2019;30(11):1955-1963.
6. Björk AB, Sjöström M, Johansson EE, et al. Women's experiences of internet-based or postal treatment for stress urinary incontinence. Qual Health Res. 2014;24(4):484-493.
7. Asklund I, Samuelsson E, Hamberg K, et al. User experience of an app-based treatment for stress urinary incontinence: Qualitative interview study. J Med Internet Res. 2019;21(3).
8. Wessels NJ, Hulshof L, Loohuis AMM, et al. User experiences and preferences regarding an app for the treatment of urinary incontinence in adult women: a qualitative study. JMIR 2020; (In press)
9. Morgan DL. Follow-up Qualitative Extensions to Core Quantitative Research Projects. In: Integrating Qualitative and Quantitative methods. 2014. p. 62–7.
10. Loohuis AM, Wessels NJ, Jellema P, et al. The impact of a mobile application-based treatment for urinary incontinence in adult women: Design of a mixed-methods randomized controlled trial in a primary care setting. Neurourol Urodyn. 2018;37:2167–76
11. Damen-van Beek Z, Wiersma T. Practice guideline 'Urinary incontinence in women' from the Dutch College of General Practitioners. https://www.nhg.org/standaarden/volledig/nhg-standaard-incontinentie-voor-urine. (Accessed 20 July 2020)
12. Dumoulin C, Hunter KF, Moore K, et al. Conservative management for female urinary incontinence and pelvic organ prolapse review 2013: Summary of the 5th International Consultation on Incontinence. Neurourol Urodyn. 2016;35:15–20.
13. Ivankova N V., Creswell JW, Stick SL. Using Mixed-Methods Sequential Explanatory Design: From Theory to Practice. Field methods. 2006;18(1):3–20.
14. Creswell, J. W., V. L. Plano Clark, M. Gutmann, et al. 2003. Advanced mixed meth-ods research designs. InHandbook on mixed methods in the behavioral and social sciences,ed. A. Tashakkori and C. Teddlie, 209–40. Thousand Oaks, CA: Sage
15 Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn. 2004;23(4):322-330.
16 Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research: A 32-item checklist for interviews and focus groups. Int J Qual Heal Care. 2018;19(6):349–57.
17. Fetters MD, Freshwater D. The 1 + 1 = 3 integration challenge. J Mixed Methods Res. 2015;9(2):115-117.

APPENDICES

Appendix 1: Supplemental methods: Randomized controlled trial

Randomized controlled trial:

From July 2015 through July 2018, we recruited 262 women for the RCT in the north of the Netherlands. Women were recruited through general practitioners, social media, and the lay press. The following inclusion criteria were used: female sex; age ≥18 years; self-reported stress, urgency, or mixed UI at least twice a week according to the Three Incontinence Questions (3IQ); wanting treatment; and access to a smartphone or tablet. Women with the following were excluded: indwelling urinary catheter, urogenital malignancy, previous surgery for UI, treatment for UI in the previous year (pharmacological or non-pharmacological), terminal or serious illness, cognitive impairment, psychiatric illness, urinary tract infection (dipstick, and if negative, dipslide or urine culture), overflow or continuous UI, pregnancy or recent childbirth (<6 months ago), or the inability to complete a questionnaire in Dutch.

After randomization, women in the intervention group received instructions to install the URinControl app on a smartphone or tablet. The app contained a step-by-step program for the self-management of UI based on Dutch GP and international guidelines for treatment of UI.[11,12] It provided information about UI, lifestyle advice, exercises to increase awareness of the pelvic floor muscles, and exercises for pelvic floor muscle therapy (PFMT) and bladder training. Depending on the type of UI identified, instructions within the app directed the user to relevant information and exercises. The app also provided reminders and graphical feedback of the number and level of exercises performed. Additional information on the development and content of this app has been reported previously.[12] Participants were free to contact their GP with any questions regarding medical aspects and/or to receive additional treatment.

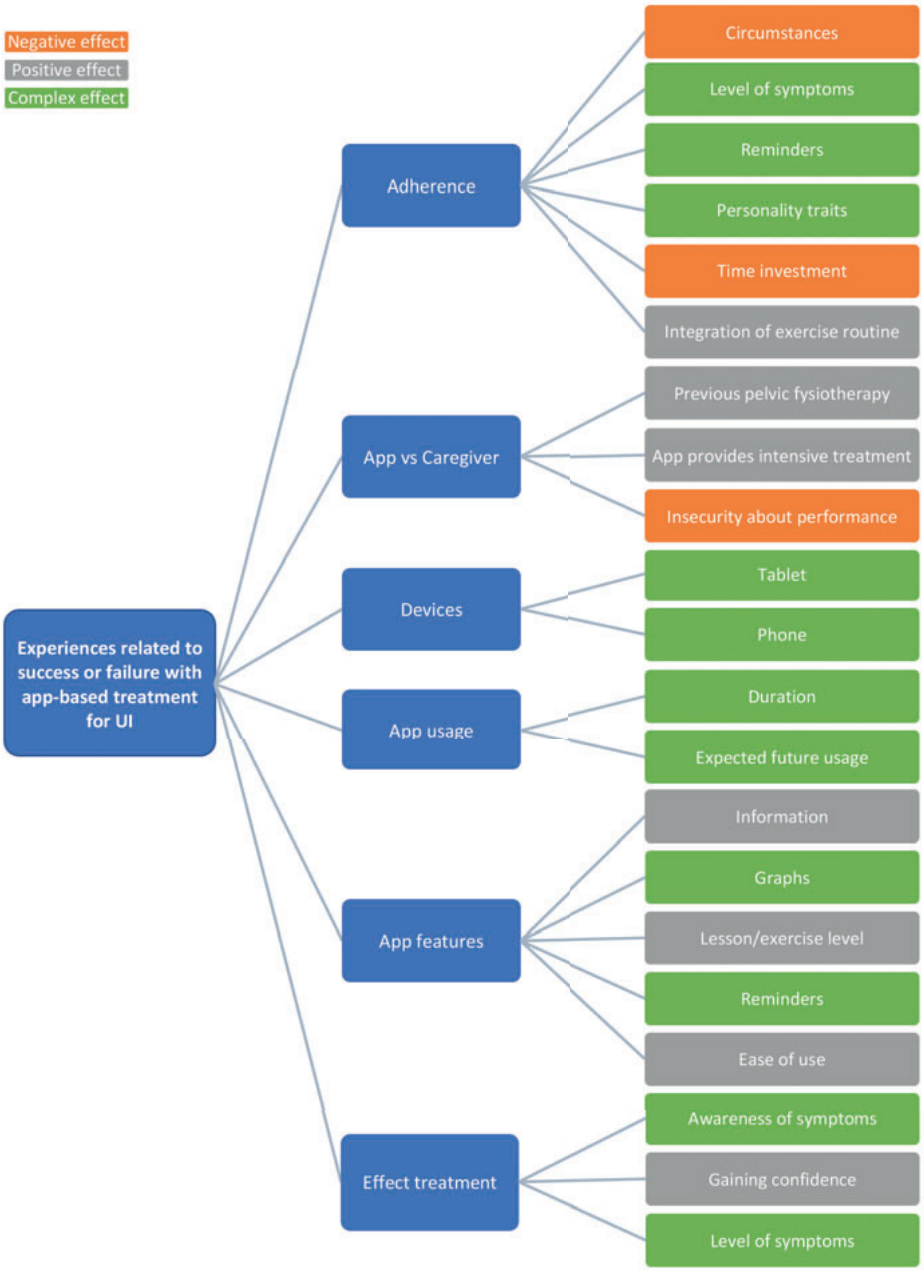
Appendix 2: Supplemental methods: Process of qualitative data analysis

Process of qualitative data analysis.

Transcripts of the telephone interviews were coded separately by two researchers (NW, LA). A consensus check was performed by NW after coding of the first 3 transcripts, showing the use of similar codes throughout the transcript. Minor adjustments to the coding tree were made accordingly. Coding continued separately and emerging new categories were regularly discussed within the research group. This was driven by an inductive approach, allowing new patterns and categories to emerge from the raw data. Interviews were conducted until no new categories emerged in three consecutive interviews. (i.e., until we had reached saturation). Broader themes emerging from the categories where discussed within the research group, resulting in a final coding tree (Figure S1). During this process, constant comparison was made with the raw data to ensure that the themes would cover all the data.

Further analysis was carried out in two stages. First, two researchers (AL, NW) focused on the coded data of all participants. Relationships between the main themes was discussed, resulting in a cross-thematic network, which was subsequently reviewed within the research group. Second, AL and NW compared and contrasted experiences in both the success and failure group, hereby re-evaluating the cross-thematic network within each group. Between-group differences in subthemes where described. The between-group differences in subthemes generated in the analysis were checked by frequency counts, which showed clear patterns matching those found in the interviews (Table 2)

Appendix 3: Figure Coding tree including major topics and subthemes



7

CHAPTER 8

General discussion

1. This Thesis

The overall aim of this thesis was to evaluate if, and for whom and how, an app-based treatment for urinary incontinence (UI) is a suitable alternative to care-as-usual in general practice.

Background

UI affects one in three women and has a significant impact on their wellbeing, but good care is complicated by challenges in help-seeking behavior, the delivery of optimal treatment, and adherence to that treatment. When considered on a large scale, this could lead to needless suffering, insufficient healthcare provision, and prohibitive costs. An app-based eHealth treatment strategy for UI could therefore offer important benefits, being able to provide an anonymous, accessible, and personalized approach, as well as structured treatments. These features of the technology could improve adherence and treatment, but they assume that eHealth is effective. Unfortunately, however, research into the (cost-) effectiveness, facilitators or barriers, and outcome predictors associated with eHealth has been scarce and often of low quality. To date, we have seen a situation where the development of new apps often comes before their evaluation or implementation strategy. Careful consideration of the effectiveness and implementation of eHealth should be a prerequisite to spending limited healthcare resources and exposing patients.

Does it work?

This thesis shows that app-based treatment for UI is non-inferior to care-as-usual in reducing UI symptoms after 4 months. Both app-based treatment and care-as-usual produced clinically relevant improvements in symptoms and quality of life after 4 and 12 months. App-based treatment is also cost-effective compared with care-as-usual, showing comparable effectiveness at lower costs for incontinence-related expenses (Chapter 4 and Chapter 5).

For whom does it work?

We personalized the decisions about app-based treatment and care-as-usual, using age, educational level, and impact on quality of life at baseline as the modifiers of treatment outcome for each treatment. We identified the treatment from which each patient was most likely to benefit and calculated the clinical relevance of that benefit. We think that this knowledge can be used by caregivers and patients to improve discussion of the benefits and drawbacks of both treatments, facilitating informed choice between app-based treatment and care-as-usual (Chapter 6).

How does it work?

The facilitators and barriers related to the success of app-based treatment were determined by semi-structured interviews with patients who had high and low responses to app-based treatment. These barriers and facilitators included *personal factors*, *app factors*, and *awareness*, although *adherence* was the main theme that connected these to treatment success. The effect of many of these factors on treatment was not set, but instead, they varied between individuals; factors could be a barrier, a facilitator, or both. For example, increased symptom awareness may be related to treatment success in one woman but to failure in another. Some factors, like graphs and reminders, did not have the facilitating effect that we expected (Chapter 7).

In conclusion

This thesis shows that app-based treatment for UI can be an effective alternative to care-as-usual that saves money at the individual and societal levels. Personalization of treatment decisions and personal consideration of facilitators and barriers can improve treatment effectiveness and implementation at the individual level.

2. Evidence-Based eHealth

2.1 Methodological challenges and choices

When considering research into eHealth, it is important to note that it is not a drug with one active ingredient; rather, it is a complex intervention that comprises many interacting components.[1,2] An app combines content and technology, requires behavior change from caregivers and patients, and can produce a variety of outcomes related to symptoms, costs, and patient experience. There is no gold standard for eHealth development and evaluation, and for complex interventions, no theoretical approach is known to be better than another.[3] This combination of complexity and technology led to important challenges that should be considered when interpreting our results.

Theoretical background of eHealth

A good theoretical understanding of how an intervention causes change can improve the design of both the intervention and its evaluation,[1] but this is still lacking for eHealth. Although it has been evaluated against the current best-practice for clinical intervention, targeting its effectiveness, there remains limited data concerning the features contributing to that effect.[4] In our study design, we therefore chose a combination of theories in the fields of pragmatic effectiveness research, process evaluation, mixing methods for health services research, and methods for telemedicine (Chapter 2).[5–12] Behavioral change was considered by some of these, but it was not our focus.

The design of our intervention, the app-based treatment, was based on both evidence and expectations. For the content, we used evidence regarding the conservative management of UI and supported this with practical patient information and the input of patients, healthcare professionals, and information technology specialists.[13-16] The technological features, however, were based on expectations of effectiveness: animations and games to improve treatment quality, reminders to improve integration in daily lives, and graphs to motivate women through feedback. The results of our process evaluation did not always support our expectations of the positive effect of these technological features. For example, the reminders and graphs were not the strong facilitators we expected, and they could even function as barriers to treatment success (Chapter 7).

When interpreting the results of our trial, it is important to consider that we must still optimize the effectiveness of app-based treatment. Further improvement may be possible by making use of evidence on behavioral change in eHealth. We learned through experience that expectations may be a valid starting point, but that there needs to be proper evaluation to discover the mechanisms and true utility as an eHealth feature. Therefore, we stress that all developers and researchers in eHealth must combine effectiveness research with a process evaluation, not only to improve their own intervention but also to fill existing knowledge gaps. Much could also be learned about behavioral change from non-health apps.

Tension between eHealth development and the need for thorough evaluation

Whereas technological advancement is an ongoing process that never stops, traditional research methods take a long time and are often rigid to maintain internal validity. A randomized controlled trial (RCT) is still the gold standard for effectiveness research, with a process evaluation necessary to gain understanding.[17] In this study we experienced tension between fast development and slow research, as well as from the mixing of different methods.

Our RCT took 7 years from grant application in 2014 to publication of the main results in 2021 (Chapter 4), and as of now, the intervention has still not been implemented. Also, we chose a fairly rigid design to maintain internal validity and did not make any substantial changes to the app during the trial period, consistent with the RCT methodology developed for drugs. We waited to conduct the process evaluation interview until after a patient had completed the trial (Chapter 7). However, within the 7-year period, there have been updates and technological advances that will have made some of our research findings outdated before they can be applied.[18] By "locking" our intervention, the attractiveness and usefulness did not develop in tandem with other apps in the field.[19] We believe this can be overcome in the future by using our results to drive new rounds of development and evaluation during implementation. However, it is not desirable nor achievable to repeat this process for every new app-based intervention.

Given the limitations of traditional research, some in the field of eHealth are advocating lower quality effectiveness research to make it faster and more responsive.[20,21] Ultimately, this is likely to impact the quality of care received by patients adversely, so it might be better to focus trials on the concepts of app-based interventions[19] and the principles underlying effectiveness.[4] If we were to study app-based treatment for UI again, this approach would require that we still assess effectiveness by focusing on an evaluation of the underlying principles. For an app, these principles could be education, self-management, and adherence, together with the components linked to these, such as informational graphics, reminders, graphs, and structured training schedules (Chapter 2). The strategies and their components could be evaluated through clinical outcomes (e.g., knowledge and self-efficacy) and usage patterns. In this way, an app and its components can be updated if the principles remain unchanged, with the results benefitting from being more generalizable and useful to the development of other apps.

Inclusion and attrition in eHealth research

Slow recruitment and higher-then-expected attrition led to a major delay in data collection in this thesis. Our research did allow us to make positive use of the target population for recruitment, but this may have negatively influenced the attrition rate. Recruitment took 3 years instead of the planned 1 year despite a realistic a priori calculation based on the available literature and our experience (Chapter 2).[22,23] When recruiting general practitioners (GPs), we did not consider their interest in the topic, which later turned out to be predictive of recruitment success.[24] However, adding recruitment through (social) media increased our recruitment rate dramatically and restored the trial's feasibility. This strategy fit our population where smartphone ownership was an eligibility criterion, and changing to this recruitment strategy had negligible impact on the sample characteristics (Chapter 3).

Attrition rates were also higher than the 20% we anticipated. When evaluating eHealth interventions, a major feature and challenge is that participants often cease usage and/or are lost to follow-up.[25] The attrition rate for care-as-usual was higher than that for app-based treatment in our trial after 4 months (29% vs 22%) and 12 months (37% vs 32%) (Chapter 5). This might indicate that attrition may result not only from the ease of discontinuation of eHealth but also from the characteristics of participants recruited for eHealth research. The increased recruitment from social media meant that we could include more women than planned beforehand and compensate for the attrition rate, resulting in an acceptable power of 78% for our main outcome measure (Chapter 4).

2.2 From expectations to evidence

An app-based treatment for UI was expected to offer numerous advantages. Here, we will discuss if these were supported by evidence.

Expectation 1: App-based treatment can lower barriers to seeking help

Apps are anonymous and easily accessible, and their wide availability creates an opportunity for greater awareness on the subject.[26] Previously identified barriers to seeking help concern thoughts about the perceived severity of disease, coping strategies, and (lack of) knowledge about treatment options.[23,27] Our process evaluation showed that the expectations of anonymity and availability of app-based treatment did motivate women to participate in the trial (Chapter 7, data not shown). During usage, the information within the app increased their awareness of coping strategies and treatment options and lowered the barriers to visiting a care professional. Furthermore, its use empowered women to start talking with friends and family about UI, which might have encouraged others to seek help. When recruiting through (social) media we focused on women seeking help for UI, regardless of whether they wanted app-based treatment or care-as-usual. The online response suggested that a lack of knowledge about UI and its treatment may be the greatest barrier to seeking help as many did not know that UI is not a normal part of aging or that effective treatments exist.

In conclusion, available qualitative evidence indicates that app-based treatment improves help-seeking behavior (Chapter 7). It can increase awareness of the condition and its treatment options while also offering an easily accessible stand-alone treatment. For this to work, women with UI need to be aware that the app exists, which can be promoted through public campaigns on social media, in lay press targeting adult women (e.g., LINDA, LIBELLE, Women's Health), via online information pages, and on the Dutch GP website (www.thuisarts.nl).

Expectation 2: An app-based treatment improves delivery of treatment

Apps can offer treatments in a structured way independent of a caregiver. Indeed, conservative treatments are highly effective for UI and are recommended by Dutch and international guidelines[13,14] but are very dependent on staff and caregiver time availabilities.[28] A recent retrospective study of routine primary care data showed that the current level of care offered by Dutch GPs is not in line with the Dutch GP guideline. In that study, GPs often failed to report the UI type (40.4%), often treated by education (17.9%), and referred excessively to pelvic floor muscle therapy (PFMT) (28.7%) and secondary care (21.7%). No treatment or referral was reported in 15.8% of cases.[29] Women receiving care-as-usual in our trial were also undertreated according to these guidelines, with 19% not visiting their GP to discuss treatment options initially; of those who did see a GP, only 68% received a specific treatment for UI and 46% of these were referrals for PFMT (Chapter 5). App-based

treatment did optimize treatment delivery by guiding patients to most treatment aspects in a structured way. Of the women randomized to app-based treatment, 98% used the app at least once, but only 9% were referred to a specialist for PFMT and only 4% received additional medication for UI.

Despite both the structure afforded by app-based treatment and the suboptimal provision of care-as-usual, our trial outcomes did not reveal superior symptom improvement with app-based treatment (Chapter 4). It could be that the structured delivery of app-based treatment was matched by other factors that increased the effectiveness of care-as-usual (e.g., better personal instructions and more commitment due to personal support) or that decreased the effects of app-based treatment (e.g., low app usage or performing exercises incorrectly). The app-based treatment itself may not have been experienced in a structured way by users, even though it was presented with that intent. Our process evaluation did give some insight and showed variations in the experiences of the app's navigability, general usability, readability, and motivational functions (Chapter 7).

In conclusion, there is no evidence to support that treatment delivery improves when using an app. Also, it appears that not all patients received their content in the structured way, as designed. We did not objectively measure how women used the app, such as how they navigated it, the features they used, and how frequently they used those features. These are interesting points that will require clarification in future research.

Expectation 3: App-based treatment improves adherence to treatment

Improved adherence to treatment could be achieved through better integration in daily life and ready access to detailed instructions.[30] Adherence is a cornerstone of maintaining effectiveness with PFMT and bladder control exercises, but it varies and declines with time.[31-34] Lack of knowledge, skills, motivation, and integration in daily life are known barriers to adherence.[34,35] By contrast, higher adherence is associated with reasonable expectations, self-efficacy, and integration in daily life, as well as higher age, education, and UI severity.[34] Recently, higher treatment uptake and adherence were shown with app-based treatments compared with postponed treatments or information provided on paper.[36-39] Adherence rates were not comparable to each other or to existing rates for care-as-usual or supervised treatment. These studies also did not investigate the underlying mechanisms further. In our mixed-methods study, adherence was the central theme related to success or failure of the app-based treatment, with all other themes both positively and negatively related to this central theme. Built-in functions sometimes did not produce the expected facilitating effects (Chapter 7). These results underline the complex nature of adherence.[40,41]

In conclusion, there is insufficient evidence to conclude that adherence can be improved by app-based treatment. To date, there has been no appropriate comparison between adherence to app-based treatment and to care-as-usual, supervised treatment, or other apps because of the marked heterogeneity in reporting and the low quality of existing study designs. Results are promising, but they also indicate that the mechanism of adherence is complex and that the addition of one technology to a treatment regimen (e.g., reminders) may not prove key to improvement.

3. Clinical Implications

Our app-based treatment was a viable alternative to care-as-usual in our study setting, but we must also consider how its implementation might affect the healthcare system and patient care?

3.1 App-based treatment in the current healthcare system

The beneficial effect of a new treatment in a study setting often lessens after implementation. This was experienced with an app-based treatment for stress UI in Sweden, which was first compared with postponed treatment in a RCT.[42] However, we anticipate that implementing our app-based treatment might lead to a larger benefit because we used care-as-usual as the control group. Compared with care-as-usual in our study, women in routine primary care typically receive PFMT less often (28% vs 68%) and are referred to secondary care more often (22% vs 1%) (Chapter 5).[29] The difference in referral rate may reflect a more active and conscious treatment choice by GPs due to their participation in our study (i.e., the Hawthorne effect).[43] Our results for app-based treatment may also be higher than expected because there can be greater motivation for patients in a study setting. Apart from that, given that the app was a stand-alone treatment in a study setting, its usage, effects, and costs should be comparable in real-world settings. The superior effectiveness and cost-effectiveness of our app-based treatment compared with care-as-usual should remain and might even increase after implementation.

An app-based treatment must be used for its benefits to be realized.[5] The Dutch eHealth monitor 2019 showed that gaps persist between offerings, usage, and usage potential. There must become a sense of urgency among patients and caregivers and a greater understanding of the added value of eHealth interventions.[44] This sense of urgency was noted by GPs, pelvic physical therapists, and patients because, as they are aware of the bottlenecks that exist in care access and delivery (e.g., lack of time, knowledge, and experience), the burden of contact with a professional, and the costs of PFMT.[11,45] There are still doubts about the added value of eHealth for UI, with a need for evidence and insecurity about the lack of personal support.[11,45] For optimal implementation, it is important to communicate the challenges of current UI care together with the evidence base for the added value of app-based treatment. Using trustworthy sources (e.g., thuisarts.nl and the

Dutch GP guideline) combined with (social) media, we showed that it is possible to send a reliable and strong message with a wide reach. Implementation requires easy access, usable technology, and transferable results to ensure optimal cooperation between the care professional, the patient, and the app.

As with any treatment, an app needs to be funded and maintained for continued use. But, on whose shoulders should this fall? Costs result from initial development and annual maintenance, which were very low for the URinControl-app, being €30,000 and €3,000, respectively.[46] Allowing for an estimated 30,000 users, costs were just €1.10 per patient per year (Chapter 5). At the same time, the app saves on the costs of GP visits, PFMT, specialist referrals, and incontinence materials for health insurers. Some of these costs are also borne by patients. A health insurer could reimburse the costs of the app, but variations in insurer policies could negatively affect the app's availability for the general population. Given that costs per patient are very low, it may be justifiable to ask the patient to pay for the app directly through an appropriate app store.

Just like the pelvic floor muscles, an app needs maintenance. This process is necessary to keep the content and technology of the app up to date as new evidence becomes available. At present, evidence-based eHealth interventions are often produced by university research groups, and because their main task is to evaluate innovations, we cannot expect them to continue maintenance. A sensible option could be to transfer the app to a company that specializes in health apps, but the potential for motivation by profit and an inadequacy of knowledge could endanger the app's cost-effectiveness. An ideal solution could be to have a university or nationwide eHealth taskforce that maintains apps for universities and/or the government. This taskforce could accommodate further maintenance and evaluation of all app-based treatments accepted for healthcare delivery. Such an approach removes the concerns about profiteering and poor knowledge of eHealth and healthcare, while being paid for by any earnings the interventions generate. Any profit gained beyond its reasonable running costs could then be made available as grants to finance further evidence-based eHealth research.

An evidence-based app can be effective, usable, funded, and maintained, yet only be one of many apps that is available for a specific disease. Patients and care professionals alike need guidance on which app to choose, but there is presently no easy to use central guidance. Medical apps have CE marks, an indicator of safety but not of effectiveness or user experience. The English *NHS Apps library* and the Dutch *GGD appstore* and *KNMG Medische app checker* offer tools to evaluate or rate separate apps.[47-50] However, for a patient or caregiver seeking an app for a specific problem, the process is complicated and time-consuming. Central guidance should aim to rate apps in terms of the user, the condition, the treatment goal, and the available treatment options. A patient and caregiver could be helped by giving advice on the best available apps related to the available treatment options, including care-as-usual, and by linking to available guidelines for a specific condition. It would be even better if this advice could be personalized, as we demonstrated in Chapter 6.

3.2 App-based treatment for the specific patient

App-based treatment is not a one-size-fits-all solution. By knowing how and for whom the app works, it is not only possible to improve an app but also for a patient to make a conscious choice between it and care-as-usual.

There is no single active ingredient in app-based treatment, but rather a complex interaction of many components. The "whom" and the "how" are entangled with each other, as exemplified by the built-in features. Many researchers and app-developers try to increase the effect of an app-based treatment for UI with features like push notifications, graphs, education, a comic character, and empathic verbal and visual instructions, as we did (Chapter 2).[39,51] Nevertheless, our mixed-methods research showed that different women could experience a feature as positive or negative in terms of treatment success. For one woman, reminders and extensive information were helpful, whereas these could have a negative effect on awareness and adherence for another (Chapter 7). This emphasizes the need to build apps that adapt to the user. Any further research to clarify the mechanism of treatment success should ensure consideration of user characteristics.

An important preconception of GPs in our trial is exemplified by the statement that "An app-based treatment is not for everyone; I don't expect our older patients or patients with lower educational levels to fare well with eHealth." Previous literature and our research did show that lower educational level was associated with lower eHealth usage and lower treatment success of eHealth, but higher age actually predicted successful app-based treatment for UI (Chapter 6).[52,53] This implies that higher age should not be perceived as a barrier, and might even facilitate treatment success, whereas educational level is an important consideration when developing and implementing an app-based treatment.

The relation between lower educational level and lower success of app-based treatment could be explained in various ways, including low health literacy or eHealth-literacy (a person's ability to understand or use an app and the included treatment), lifestyle or occupation (integration of the app in daily life), access to technological and medical services (technological ease of use and ease of asking for support), and self-efficacy (affecting treatment uptake and continuation). These clearly require further evaluation, possibly during the implementation phase, by assessing usage patterns and treatment effects in relation to educational level and other patient characteristics. In the meantime, developers should consider tailoring app-based treatment to patients with low-literacy, improving the app's availability, readability, and usability. Caregivers should account for this characteristic, not by withholding the treatment, but by offering optional extra support or explanation.

The greatest challenge to wide implementation might be to change the views of caregivers and to resolve any misconceptions that lead to biased treatment decisions. A decision tool, as described in Chapter 6, could overcome these issues by offering objective insight into

patient characteristics and expected treatment outcomes. Furthermore, the guidance of this tool does not necessarily exclude a less favorable option and could lead to the more conscious use of that option with extra support from the caregiver.

4. Societal impact

The true outcome of research is determined by its influence on society, and by the changes it ignites.[54] Previous sections of this chapter have focused on the potential impact of the app for UI on science, health, economy, policy, and technology. Here, the cultural and societal impacts of the app are considered.

Apart from the direct comparison between app-based treatment and care-as-usual for UI, the app could improve care-as-usual itself. Suboptimal delivery of care-as-usual for UI has been a central theme of this thesis, being a major reason for developing the app. We know that effective conservative treatment options are not delivered optimally and that GPs often do not adhere to guidelines,[28,29] probably because of a lack of knowledge, time, or awareness.[55,56] However, these have been targeted in previous research without dramatically improving care.[13,56] It may be, and this is stated with some reservations, that suboptimal care results from ignorance or trivializing of UI among GPs and from a passive attitude among patients. From the GP's perspective, UI does not kill a patient, suboptimal care for UI produces no consequential adverse outcomes, and there may be much more urgent problems that are easier to discuss or fix in daily practice. Many patients already experience barriers to seeking help and have little knowledge about existing treatments; therefore, only a few would demand sufficient treatment from their GP. Increased availability of app-based treatment and a public campaign to propagate this could ignite meaningful change, raising awareness about both UI and the availability of effective conservative treatments. This may prompt GPs to realize the urgency of the unmet need for this problem, but more importantly, it could empower women to seek help and demand appropriate treatment for UI.

The greatest challenge of all will be to reduce the taboo and embarrassment associated with UI, which at present, are significantly higher than for depression or cancer.[57] UI is not a common topic of conversation, possibly accounting for the lack of knowledge about UI among patients and caregivers.[23,57] During recruitment, the exponential increase in the number of women subscribing through (social) media may have addressed both the lack of knowledge ("Did you know a treatment for UI exists?") and the taboo and embarrassment (signing up online instead of asking a health care provider). App-based treatment can reach many more women online, gradually increasing knowledge on the availability of treatments and creating better awareness of the condition. Women in our study mentioned that the app made them more aware of the condition ("I am not the only one," "UI is not a normal process of aging," and "I now know that I can influence my UI symptoms") and encouraged some to start talking to other women about the app and UI. To further stimulate this process, the app could be connected to an anonymous

platform where women can share their training progress, offer support to each other, and share their experiences of treatment and UI. Societal taboos need to be broken before we reach a situation where women readily put their incontinence material at the top of their shopping chart, freely discuss the condition as they might for any other common condition, and dare we dream, share their achievements on Facebook, Twitter, or Instagram!

5. Future Research

5.1 App-based treatment in real-life

Implementing app-based treatment requires an ongoing process of evaluation and development with large-scale data collection. This evaluation can focus on validating effectiveness, clarifying the mechanisms of usage and treatment success, and assessing long-term engagement and effectiveness. These evaluations need to be based on measures of patient characteristics, treatment adherence, app usage, app usability, and technological challenges. With this knowledge, further content and technological developments can follow to improve the effectiveness, usability, and uptake of the app among different patient groups (e.g., low literacy, older and younger, and for prevention) and in different settings (e.g., at home, in primary care, and in secondary care). Evaluation and development can then be repeated.

5.2 App-based treatment with a broader perspective

In this thesis, we focused on the app as a stand-alone treatment, but in a real-world setting, any app-based treatment will intertwine with the healthcare system and existing technology. Thus, it would be interesting to study if and how engagement with these fields could benefit the patient.

The involvement of care professionals through blended care could effectively combine the support and feedback provided by a professional with the structure and accessibility of an app-based treatment. For this to happen, it would be critical for information on the training progress to be easily transferable and for caregivers to be aware that the app-based treatment exists. It would be interesting to study the influence of blended care on treatment effectiveness, treatment experience, and app usage. A stepped-wedge or cross-over design would be suited to this research aim.

We can learn to improved engagement with eHealth technology from popular apps like Candy Crush, Strava, and Ommetje. Anonymous connection to social media (“Your symptoms improved one drop this month! Share it now with your friends on Facebook”) and gamification (“Great job, you performed pelvic floor exercises 7 days in a row, you receive a gold medal”) could further change behavior and reduce taboo. Engagement with the technology could be studied on the log data level, allowing assessments of adherence and of user pathways.

6. General Conclusion

App-based treatment for UI is a viable alternative to care-as-usual in terms of effectiveness and cost-effectiveness, and at a personal level, its treatment effect could be improved by personalizing treatment decisions and by giving consideration to the facilitators and barriers faced by individuals. Implementing the app will provide an alternative treatment choice for GPs and their patients, potentially lowering treatment barriers and improving treatment delivery and adherence for many women with UI. By raising awareness of UI, this could also improve the quality of care-as-usual and help to lessen the taboo surrounding the condition. However, further research is still needed to improve the app-based treatment itself, to improve treatment personalization, and to unravel how the treatment works. Finally, there is a need for improved central guidance and maintenance to offer a better solution for long-term implementation and for the application of evidence-based eHealth.

REFERENCES

1. Craig P, Dieppe P, Macintyre S, Mitchie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: The new Medical Research Council guidance. Bmj [Internet]. 2008;337(7676):979–83. Available from: http://dx.doi.org/doi:10.1136/bmj.a1655
2. Oakley A, Strange V, Bonell C, Allen E, Stephenson J. Process evaluation in randomised controlled trials of complex interventions. Br Med J. 2006;332(7538):413–6.
3. O'Cathain A, Croot L, Duncan E, Rousseau N, Sworn K, Turner KM, et al. Guidance on how to develop complex interventions to improve health and healthcare. BMJ Open. 2019;9(8):1–9.
4. Gemert-Pijnen, van, L., Sanderman, R., Kelders, S. M. & Kip H. eHealth Research, Theory and Development: A Multi-Disciplinary Approach [Internet]. 1st ed. Routledge, Taylor and Francis group; 2018. 336 p. Available from: http://library1.nida.ac.th/termpaper6/sd/2554/19755.pdf
5. Ossebaard HC, Van Gemert-Pijnen L. EHealth and quality in health care: Implementation time. Int J Qual Heal Care. 2016;28(3):415–9.
6. Hulscher MEJL, Laurant MGH, Grol RPTM. Process evaluation on quality improvement interventions. Qual Saf Heal Care. 2003;12(1):40–6.
7. Caffery LJ, Martin-Khan M, Wade V. Mixed methods for telehealth research. J Telemed Telecare. 2017;23(9):764–9.
8. Zhang W, Creswell J. The use of mixing procedure of mixed methods in health services research. Med Care. 2013;51(8):51–7.
9. Kidholm K, Clemensen J, Caffery LJ, Smith AC. The Model for Assessment of Telemedicine (MAST): A scoping review of empirical studies. J Telemed Telecare. 2017;23(9):803–13.
10. Ford I, Norrie J. Pragmatic Trials. N Engl J Med. 2016;375(5):454–63.
11. Wessels NJ, Hulshof L, Loohuis AMM, van Gemert-Pijnen L, Jellema P, van der Worp H BM. User experiences and preferences regarding an app for the treatment of urinary incontinence in adult women: a qualitative study. J Med Internet Res. 2020;(in press).
12. van Gemert-Pijnen JEWC, Nijland N, van Limburg M, Ossebaard HC, Kelders SM, Eysenbach G, et al. A holistic framework to improve the uptake and impact of eHealth technologies. J Med Internet Res. 2011;13(4).
13. Damen-van Beek Z, Wiersma T. Practice guideline 'Urinary incontinence in women' from the Dutch College of General Practitioners. Ned Tijdschr Geneeskd. 2016;160:D674.
14. Abrams P, Andersson K-E, Apostolidis A, Birder L, Bliss D, Brubaker L, et al. 6th International Consultation on Incontinence. Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence. Neurourol Urodyn. 2018 Sep;37(7):2271–2.
15. Nederlands Huisartsen Genootschap. Thuisarts.nl [Internet]. [cited 2021 Feb 19]. p. urineverlies bij vrouwen. Available from: https://www.thuisarts.nl/urineverlies-bij-vrouwen
16. Slieker-ten Hove MC. Verborgen vrouwenleed. Uitgeverij Boekscout.nl; 2015. 274 p.
17. Liu JLY, Wyatt JC. The case for randomized controlled trials to assess the impact of clinical information systems. J Am Med Informatics Assoc. 2011;18(2):173–80.
18. Riley WT, Glasgow RE, Etheredge L, Abernethy AP. Rapid, responsive, relevant (R3) research: a call for a rapid learning health research enterprise. Clin Transl Med. 2013;2(1):1–6.
19. Mohr DC, Schueller SM, Riley WT, Brown CH, Cuijpers P, Duan N, et al. Trials of intervention principles: Evaluation methods for evolving behavioral intervention technologies. J Med Internet Res. 2015;17(7).
20. Pham Q, Wiljer D, Cafazzo JA. Beyond the randomized controlled trial: A review of alternatives in mhealth clinical trial methods. JMIR mHealth uHealth. 2016;4(3):1–14.

21. Kumar S, Nilsen WJ, Abernethy A, Atienza A, Patrick K, Pavel M, et al. Mobile health technology evaluation: The mHealth evidence workshop. Am J Prev Med [Internet]. 2013;45(2):228–36. Available from: http://dx.doi.org/10.1016/j.amepre.2013.03.017

22. Nederlands Instituut voor Onderzoek van de Gezondheidszorg. Zorgregistraties eerste lijn/jaarcijfers aandoeningen huisartsenregistraties [Internet]. [cited 2021 Feb 19]. p. Urine-Incontinentie. Available from: https://www.nivel.nl/nl/nivel-zorgregistraties-eerste-lijn/jaarcijfers-aandoeningen-huisartsenregistraties

23. Visser E, De Bock GH, Kollen BJ, Meijerink M, Berger MY, Dekker JH. Systematic screening for urinary incontinence in older women: Who could benefit from it? Scand J Prim Heal Care. 2012;30:21–8.

24. van der Worp H, Loohuis AMM, Flohil IL, Kollen BJ, Wessels NJ, Blanker MH. Recruitment through media and general practitioners resulted in comparable samples in an RCT on incontinence. J Clin Epidemiol. 2020 Mar 1;119:85–91.

25. Eysenbach G. The law of attrition. J Med Internet Res. 2005;7(1):1–9.

26. Björk AB, Sjöström M, Johansson EE, Samuelsson E, Umefjord G. Women's experiences of internet-based or postal treatment for stress urinary incontinence. Qual Health Res. 2014;

27. Teunissen D, van Weel C, Lagro-Janssen T. Urinary incontinence in older people living in the community: Examining help-seeking behaviour. Br J Gen Pract [Internet]. 2005 Oct [cited 2020 Nov 10];55(519):776–82. Available from: /pmc/articles/PMC1562332/?report=abstract

28. Albers-Heitner P, Berghmans B, Nieman F, Lagro-Janssen T, Winkens R. Adherence to professional guidelines for patients with urinary incontinence by general practitioners: A cross-sectional study. J Eval Clin Pract. 2008;14(5):807–11.

29. Schreuder MC, van Merode NAM, Oldenhof AP, Groenhof F, Koningsveld-Kortekaas MF, Maagdenberg H, van der Wouden H, van der Worp H BM. Reviewing primary care diagnostic pathways and treatment process in Dutch women with incontinence. (Submitted Soon). :1–18.

30. Firet L, Teunissen D, Verhoeks C, Lagro-Janssen A. Expectations regarding eHealth among women with stress urinary incontinence. [cited 2019 Feb 1]; Available from: https://doi.org/10.1007/s00192-018-3849-2

31. Dumoulin C, Hunter KF, Moore K, Bradley CS, Burgio KL, Hagen S, et al. Conservative management for female urinary incontinence and pelvic organ prolapse review 2013: Summary of the 5th International Consultation on Incontinence. Neurourol Urodyn. 2016;35:15–20.

32. Bo K, Talseth T. Long-term effect of pelvic floor muscle exercise 5 years after cessation of organized training. Obstet Gynecol. 1996;87(2):261–5.

33. Lagro-Janssen T, Van Weel C. Long-term effect of treatment of female incontinence in general practice. Br J Gen Pract. 1998;48(436):1735–8.

34. Borello-France D, Burgio KL, Goode PS, Ye W, Weidner AC, Lukacz ES, et al. Adherence to Behavioral Interventions for Stress Incontinence: Rates, Barriers, and Predictors. Phys Ther [Internet]. 2013 Jun 1 [cited 2020 Nov 10];93(6):757–73. Available from: https://academic.oup.com/ptj/article/93/6/757/2735358

35. Chantale Dumoulin, 1, 2* Jean Hay-Smith, 3, 4 Helena Frawley, 5, 6 Doreen McClurg, 7 Dianne Alewijnse, 8 Kari Bo 9, Kathryn Burgio, 10, 11 Shu-Yueh Chen, 12 Pauline Chiarelli, 13 Sarah Dean, 14 Suzanne Hagen, 15 Julia Herbert 16, Aishath Mahfooza, 17 Frances Mair, 18 Diane Stark 19 and Marijke Van Kampen20. 2014 consensus statement on improving pelvic floor muscle training adherence: International Continence Society 2011 State-of-the-Science Seminar. Neurourol Urodyn. 2015;34:600–5.

36. Carrión Pérez F, Moreno MSR, Córdoba LC, Romero Garrido MC, Tirado LQ, Montes IG. Telerehabilitation to treat stress urinary incontinence. Pilot study. Med Clínica (English Ed [Internet]. 2015;144(10):445–8. Available from: http://dx.doi.org/10.1016/j.medcle.2014.05.010

37. Kinouchi K, Ohashi K. Smartphone-based reminder system to promote pelvic floor muscle training for the management of postnatal urinary incontinence: Historical control study with propensity score-matched analysis. PeerJ. 2018;2018(2).

38. Asklund I, Nyström E, Sjöström M, Umefjord G, Stenlund H, Samuelsson E. Mobile app for treatment of stress urinary incontinence: A randomized controlled trial. Neurourol Urodyn. 2017;36(5):1369–76.

39. Araujo CC, Marques ADA, Juliato CRT. The Adherence of Home Pelvic Floor Muscles Training Using a Mobile Device Application for Women With Urinary Incontinence: A Randomized Controlled Trial. Female Pelvic Med Reconstr Surg [Internet]. 2019 [cited 2019 Feb 1];00:00–00. Available from: www.fpmrs.net

40. E.M. S, J.J. K. Patient compliance with exercise: Different theoretical approaches to short-term and long-term compliance. Patient Educ Couns [Internet]. 1991;17(3):191–204. Available from: http://www.embase.com/search/esults?subaction=viewrecord&from=export&id=L21237642%0Ahttp://dx.doi.org/10.1016/0738-3991(91)90060-I

41. Jay S, Litt IF, Durant RH. Compliance with therapeutic regimens. J Adolesc Heal Care. 1984;5(2):124–36.

42. Rygh P, Asklund I, Samuelsson E. Real-world effectiveness of app-based treatment for urinary incontinence: a cohort study. BMJ Open. 2021;11(1):e040819.

43. Sedgwick P, Greenwood N. Understanding the hawthorne effect. BMJ (Online). 2015. p. 351:h4672.

44. Wouters M, Huygens M, Voogdt H, Meurs M, de Groot J, Lamain A, et al. Samen aan zet! eHealth-monitor 2019. 2019;

45. Firet L, De Bree C, Verhoeks CM, Teunissen DAM, Lagro-Janssen ALM. Mixed feelings: general practitioners' attitudes towards eHealth for stress urinary incontinence-a qualitative study. [cited 2019 Feb 1]; Available from: https://doi.org/10.1186/s12875-019-0907-x

46. Lastovetska A. App development cost: Understand your budget to build powerful apps [Internet]. 2021 [cited 2021 Feb 19]. Available from: https://mlsdev.com/blog/app-development-cost

47. National Health Service. NHS Apps Library - NHS [Internet]. NHS Apps Library. [cited 2019 Feb 27]. Available from: https://www.nhs.uk/apps-library/

48. Gemeentelijke gezondheidsdienst. GGD appstore [Internet]. Available from: https://www.ggdappstore.nl/Appstore/Homepage/Sessie,Medewerker,Button

49. KNMG. Medische App Checker : beoordeling van medische apps. 2016;1–20.

50. Loohuis A, Chavannes N. Medical apps; Care for the future? [Dutch]. Huisarts Wet. 2017;60:440–3.

51. Latorre GFS, de Fraga R, Seleme MR, Mueller C V., Berghmans B. An ideal e-health system for pelvic floor muscle training adherence: Systematic review. Neurourol Urodyn [Internet]. 2018 Oct 30 [cited 2018 Dec 11]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/30375056

52. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: An updated systematic review. Ann Intern Med. 2011;155(2):97–107.

53. Lindh A, Sjöström M, Stenlund H, Samuelsson E. Non-face-to-face treatment of stress urinary incontinence: predictors of success after 1 year. Int Urogynecol J. 2016;

54. Holmberg K, Bowman S, Bowman T, Didegah F, Kortelainen T. What Is Societal Impact and Where Do Altmetrics Fit into the Equation? J Altmetrics. 2019;2(1):1–11.

55. Swanson JG, Skelly J, Hutchison B, Kaczorowski J. Urinary incontinence in Canada. 2002;48:86–92.

56. Gerrits M, Avery T, Lagro-Janssen A. Urinary incontinence management in women: Audit in general practice. J Eval Clin Pract. 2008;14(5):836–8.

57. Elenskaia K, Haidvogel K, Heidinger C, Doerfler D, Umek W, Hanzal E. The greatest taboo: Urinary incontinence as a source of shame and embarrassment. Wien Klin Wochenschr. 2011;123(19–20):607–10.

Scientific summary

Nederlandse samenvatting

Laymen's summary/Lekensamenvatting

Scientific summary

Background

Urinary incontinence affects one in three women and has a large impact on their wellbeing. Good incontinence care is complicated by challenges related to help-seeking behavior, the delivery of complete and optimal treatment, and adherence to this treatment. This may lead to needless suffering, insufficient healthcare, and unnecessary high costs on a large scale. An eHealth strategy could offer numerous advantages: an app-based treatment for urinary incontinence is anonymous and accessible, it offers treatments in a structured way and it has the technology to improve adherence and personalize treatment. However, the effectiveness of eHealth is not a given fact.

Research into (cost-)effectiveness, facilitators or barriers and predictors is scarce and often of low quality. Unfortunately, the development of new applications often comes first and evaluation and implementation lag behind. Careful consideration of effect and implementation in eHealth is needed before the money is spent and patients are exposed.

Results

This thesis shows that the app-based treatment for urinary incontinence is non-inferior to care-as-usual in reducing urinary incontinence symptoms after 4 months. Both app-based treatment and care-as-usual lead to clinically relevant improvement of symptoms and quality of life after 4 months. An app-based treatment is cost-effective in comparison to care-as-usual, as it shows comparable effectiveness at lower costs for incontinence-related expenses after 12 months. (Results randomized controlled trial, chapter 4 and 5)

We personalized the treatment decision between app and care-as-usual. We identified age, educational level and impact on quality of life at baseline as modifiers for treatment outcome, predicting outcome dependent on the type of treatment. Then, for each specific patient, we identified from which treatment type this patient would benefit most, and calculated the clinical relevance of this benefit. This knowledge can be used by a caregiver and a patient to improve their discussion of the benefits and drawbacks of both treatments, before choosing between app-based treatment or care-as-usual. (Chapter 6, personalized prediction randomized controlled trial)

We identified facilitators and barriers for the success of app-based treatment through semi-structured interviews with patients showing high and low responses to app-based treatment. The identified facilitators and barriers were related to *personal factors, app factors,* and *awareness. Adherence* was the main theme connecting these barriers and facilitators to treatment success.

The effect of the factors on treatment was not set but varied between individuals; factors could act as a barrier, a facilitator, or both. For example, increased awareness of symptoms could be related to treatment success in one woman, but failure in the other. Some factors, like graphs and reminders, did not have the facilitating effect on treatment as was expected beforehand. (Chapter 7, sequential explanatory mixed-methods design)

General conclusion and recommendations

An app-based treatment for urinary incontinence is a viable alternative to care-as-usual in terms of effectiveness and cost-effectiveness, and its treatment effect on a personal level could be further improved by personalization of treatment-decision and personal consideration of facilitators and barriers.

The implementation of the app offers an alternative treatment option for general practitioners and their patients. It lowers barriers to treatment and could improve the delivery of, and adherence to, treatment for many women with urinary incontinence. By raising awareness on urinary incontinence, the implementation might also improve the quality of care-as-usual and lower taboo.

Future research is needed to further improve the app-based treatment itself, to improve the personalization of treatment, and to unravel processes of treatment effect. For the urinary incontinence app-based treatment in specific and for medical apps in general, central guidance and maintenance should be considered to offer a solid solution for long-term implementation and application of evidence-based eHealth in the future.

Nederlandse samenvatting

Achtergrond

Ongewild urineverlies komt voor bij 1 op de 3 vrouwen en heeft een grote invloed op hun kwaliteit van leven. Goede behandeling van ongewenst urineverlies kent verschillende uitdagingen. Zo zijn er barrières om hulp te vragen, is de geleverde zorg vaak niet optimaal en is therapietrouw heel wisselend. Dit kan leiden tot onnodig leed, inefficiëntie van de zorg en onnodig hoge kosten op grote schaal. Een app-behandeling van ongewenst urineverlies zou verschillende voordelen kunnen bieden. Een app is anoniem en makkelijk beschikbaar. Daarnaast komen alle aspecten van een behandeling in de app gestructureerd aan bod. Verder biedt de technologie mogelijkheden om herinneringen in te bouwen voor het verbeteren van therapietrouw, of om de behandeling te personaliseren. Echter, deze voordelen liggen in de lijn der verwachting, maar zijn nog niet bewezen.

Er is weinig onderzoek gedaan naar de werkzaamheid, kosten, faciliterende en belemmerende factoren en predictoren voor succes van een app-behandeling voor urineverlies. Er is meer ontwikkeling en implementatie dan goede evaluatie. Toch is goed onderzoek naar effect en implementatie van een app-behandeling belangrijk, want anders leidt het tot onnodige kosten en suboptimale zorg.

Resultaten

Dit proefschrift laat zien dat een app-behandeling voor ongewild urineverlies niet inferieur is in vergelijking met standaard zorg voor het verlagen van urineverlies na 4 maanden. Zowel de app-behandeling als standaard zorg leiden tot klinisch relevante verbetering van ernst van urineverlies en kwaliteit van leven na 4 maanden. De app-behandeling is kosteneffectief in vergelijking tot standaard zorg, want bij vergelijkbare effectiviteit zijn de kosten lager na 12 maanden.

We personaliseerden de keuze tussen app-behandeling en standaard zorg. Op basis van leeftijd, opleidingsniveau en impact op kwaliteit van leven voorspelden we voor elke patiënt het verschil in het verwachte resultaat tussen beide behandeling. Vervolgens bepaalden we voor iedere patiënt welke behandeling tot het beste resultaat zou leiden, en of het verschil met de andere behandeling ook merkbaar was voor de patiënt zelf (klinisch relevant). Met deze kennis kunnen patiënt en zorgverlener een betere afweging maken tussen de voor- en nadelen van beide behandelingen.

Op basis van interviews bij patiënten die sterke verbetering en patiënten die sterke verslechtering van urineverlies na app-behandeling ervaarden, onderzochten we faciliterende en belemmerende factoren voor het succes van de app-behandeling. Uit deze interviews kwamen de thema's *persoonlijke factoren*, *app factoren* en *bewustzijn* naar voren. *Therapietrouw* was het overkoepelende thema dat alle factoren verbond met het succes

van de behandeling. Of een factor een positief of negatief effect had lag niet vast, maar verschilde tussen de patiënten. Zo kon dezelfde factor bij de een positief bijdragen aan behandeleffect en bij de ander juist negatief. Een voorbeeld was een verhoogd bewustzijn van klachten, dat bij de ene vrouw leidde tot betere therapietrouw terwijl het voor de ander juist confronterend was. Opvallend was ook dat grafieken en herinneringen niet altijd het positieve effect hadden dat we hadden verwacht. Soms was het effect ook belemmerend.

Algemene conclusie en aanbevelingen

Een app-behandeling voor ongewild urineverlies is een kosteneffectief alternatief voor standaard zorg. Het behandeleffect kan op persoonlijk niveau verder verbeteren door personaliseren van de behandelkeuze en het per persoon afwegen van faciliterende en belemmerende factoren.

Door implementatie van de app is er een nieuwe behandeloptie voor vrouwen met urineverlies en hun zorgverleners. De app verlaagt de drempel om hulp te vragen en de toepassing van geschikte behandeling en kan de therapietrouw mogelijk verbeteren. Implementatie kan het bewustzijn en de kennis rondom urineverlies verhogen, het taboe verlagen en zo mogelijk ook de standaard zorg verbeteren.

Verder onderzoek is nodig om de app-behandeling verder te ontwikkelen, om personalisatie van behandeling te verbeteren en om het behandel-effect en onderliggende mechanismen beter te begrijpen. Voor de app-behandeling voor urineverlies specifiek én voor medische apps in het algemeen is centrale sturing en onderhoud mogelijk een oplossing voor het optimaliseren van implementatie en uitvoering van evidence-based eHealth op de lange termijn.

Laymen's summary/Lekensamenvatting

Samenvatting van dit proefschrift

Waarom dit onderzoek? Urineverlies komt voor bij 1 op de 3 vrouwen, van wie een groot deel het lastig vindt om hulp te vragen. Bekkenbodemspieroefeningen en blaastraining zijn goede behandelingen, maar kosten veel tijd en geld en de therapietrouw wisselt. Een app-behandeling is laagdrempelig, goedkoper en verbetert mogelijk therapietrouw. Er bestaan al meer dan 100 apps voor urineverlies, maar hun werkzaamheid is nauwelijks onderzocht. Het is belangrijk om te weten of zo'n app niet slechter werkt dan de bestaande zorg, voordat vrouwen deze gaan gebruiken.

We vroegen ons het volgende af: Werkt een app voor de behandeling van urineverlies net zo goed als standaard zorg? Is de app goedkoper? Voor wie werkt de app het beste?

Dit proefschrift laat zien dat een app-behandeling even goed werkt én goedkoper is dan standaard zorg. Omdat sommige vrouwen baat kunnen hebben bij een app en sommigen meer bij persoonlijke begeleiding maakten we een keuzehulp. Hiermee kan een patiënt zelf berekenen door welke behandeling haar urineverlies waarschijnlijk het meest verbetert: de app, standaard zorg, of beide evenveel. Verder vergeleken we vrouwen met veel succes en met juist weinig succes van app-behandeling. We vroegen hen welke factoren zij belangrijk vonden voor dit resultaat. Hieruit blijkt dat dit voor iedere vrouw verschillend is. Therapietrouw vonden zij de belangrijkste factor voor succes. Daarnaast blijkt dat de factoren waarvan succes werd verwacht (zoals grafieken en herinneringen) lang niet voor iedereen even goed werkten.

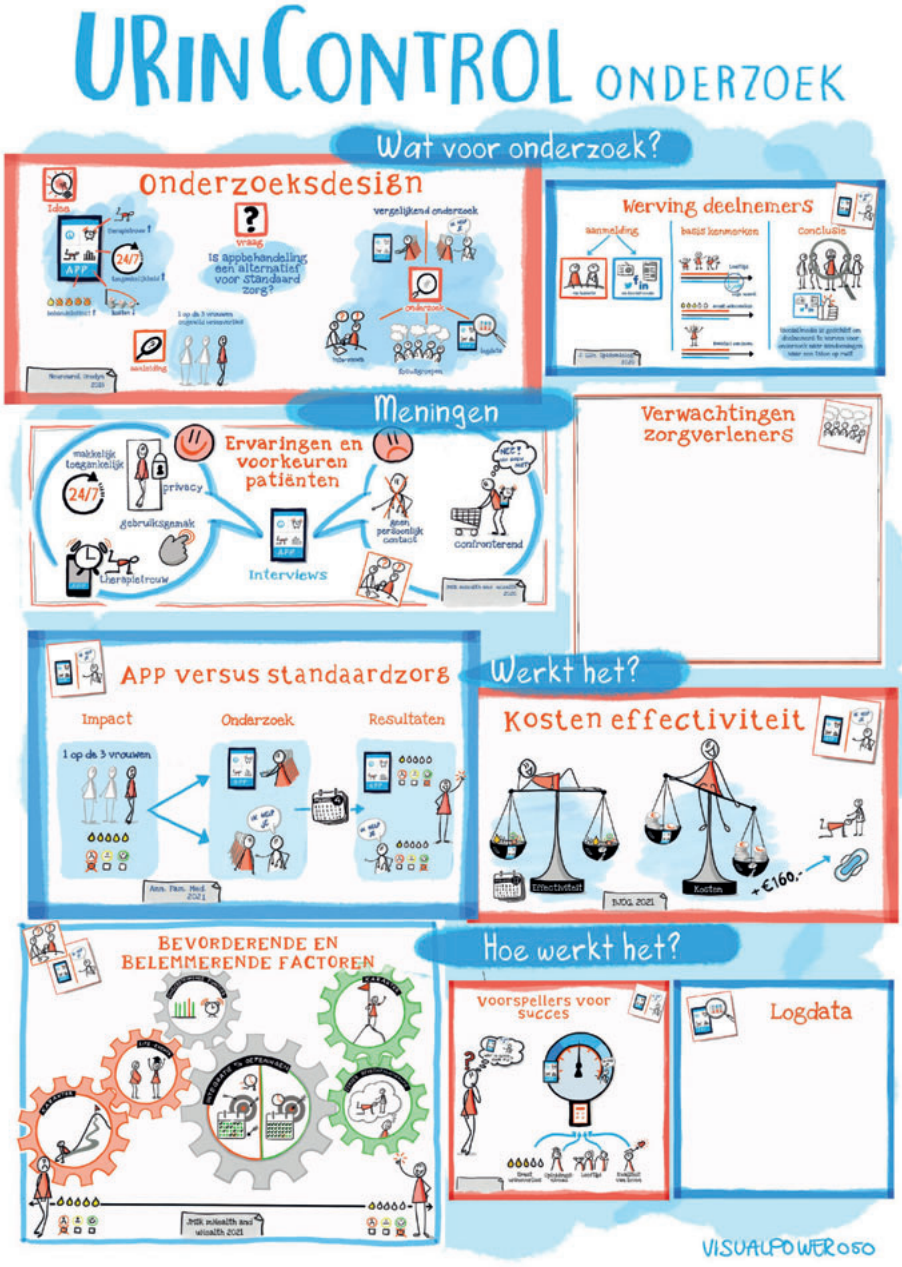
Aanbevelingen naar aanleiding van dit proefschrift:
(1) URinControl-app beschikbaar voor alle vrouwen in Nederland.
(2) Verder onderzoek: naar app-gebruik, persoonlijke factoren en de werking van eHealth.
(3) Centraal punt voor onderhoud en implementatie van wetenschappelijk bewezen eHealth.

URinControl in beeld: In de praatplaat (volgende pagina) vindt u alle onderdelen van het onderzoek in één illustratie. Op de website www.urincontrol.nl vindt u de lekensamenvatting in de vorm van een filmpje.

DE URinControl-APP

De app werkt en is een goed alternatief voor standaard zorg. Daarom is hij nu via URinControl.online beschikbaar voor alle vrouwen in Nederland met urineverlies. Dankzij de samenwerking met het platform Gezondheidsmeter.nl is de app gratis en beveiligd. Met hulp van een subsidie van ZonMw kreeg de app een update en kunnen we de werkzaamheid van de app nu onderzoeken in de algemene populatie.

De app is in de landelijke media verschenen, zo hopen we deze behandeling onder de aandacht te brengen bij zoveel mogelijk vrouwen met urineverlies.


URIN CONTROL ONDERZOEK
Wat voor onderzoek?
Onderzoeksdesign
Idee
vraag
Is appbehandeling een alternatief voor standaard zorg?
vergelijkend onderzoek
Werving deelnemers
aanmelding
basis kenmerken
conclusie
Meningen
Ervaringen en voorkeuren patiënten
makkelijk toegankelijk
24/7
privacy
gebruiksgemak
therapietrouw
Interviews
geen persoonlijk contact
confronterend
Verwachtingen zorgverleners
APP versus standaardzorg
Impact
Onderzoek
Resultaten
1 op de 3 vrouwen
Werkt het?
Kosten effectiviteit
Effectiviteit
Kosten
€160,-
BEVORDERENDE EN BELEMMERENDE FACTOREN
Hoe werkt het?
Voorspellers voor succes
Logdata
VISUALPOWER050

List of Publications

Presentations

Prizes

Research Institute for Health SHARE

List of publications, presentations and prizes

Other publications

- te Brummelstroete GH, Loohuis AMM, Wessels NJ, Westers HC, van Summeren JJGT, Blanker MH. Scientific evidence for pelvic floor devices presented at conferences: An overview. *Neurourology and Urodynamics*. 2019;38: 1958-1965. https://doi.org/10.1002/nau.24099
- Wessels NJ, Hulshof L, Loohuis AMM, van Gemert-Pijnen L, Jellema P, van der Worp H, Blanker MH. User Experiences and Preferences Regarding an App for the Treatment of Urinary Incontinence in Adult Women: Qualitative Study. *Journal of Medical Internet Research mHealth and uHealth*, 2020;*8*(6):e17114. https://doi.org/10.2196/17114
- van der Worp H, Schuch G. A., Loohuis AMM, van Uum RT, Willemsen RTA, Cals JWL, Blanker MH. Intrinsic motivation of GPs was not related to recruitment success, whereas interest in the study topic was. Sep 2020, In: *Journal of Clinical Epidemiology*. 125, p. 158-160 3 p. https://doi.org/10.1016/j.jclinepi.2020.06.009
- Zelfmanagement van urine incontinentie met een app. Loohuis AMM et al. Huisarts & Wetenschap, 2021. Inclusief interview in podcast van Huisarts en Wetenschap.
- Boekrecensie Praktische huisartsgeneeskunde- Urogynaecologie. Loohuis AMM. *Huisarts & Wetenschap*, 2021
- Beschouwing Medische Apps; zorg voor de toekomst? Loohuis AMM, Chavannes NH. *Huisarts & Wetenschap*, 2017
- Medicatie heeft geen invloed op passage uretersteen. Loohuis AMM, Blanker MH. *Nederlands Tijdschrift voor Geneeskunde*, 2015
- App voor behandeling incontinentie. Loohuis AMM. *Huisarts & Wetenschap*, 2015

Scientific presentations and workshops (abstract presentations excluded)

2016 Workshop e-health in Pelvic floor disorders, ICS annual meeting, Tokyo, Japan. Anne Loohuis: from cool tool to evidence based eHealth

2019 Workshop eHealth for incontinence, ICS Annual Meeting, Gothenburg, Sweden. Involved in content and preparation, unfortunately not able to attend

2021 Parallelsession NHG-Conference "General practice 2.0", eHealth & urology. Originally planned 11 december 2020, delayed due to corona.

Prizes

2015 Winner workshop research communication at SHARE-day

2016 Winner professor Huygenprijs, LOVAH congres, *Best research proposal by a dutch general practice trainee*

2020 SHARE PhD Top Publication Award *Noninferiority app-based treatment (chapter 3) in Annals of Family Medicine 2021.*

2020 Best abstract in conservative management category: e-Health at ICS annual Meeting.

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(supervisors are between brackets)

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(prof M Hagedoorn, dr MA Tuinman)

Minh A
Mental health, education and work in Canada, the Netherlands, and the United States; a comparative, life course investigation
(prof U Bültmann, dr CB McLeod, prof SA Reijneveld, dr M Guhn)

Marcus-Varwijk AE
Perspectives on health and health promotion in community-dwelling older people; a mixed-methods study
(prof JPJ Slaets, prof AV Ranchor, dr CHM Smits, dr TLS Visscher)

Bochane MI
Uniform screening for atypical language development in Dutch child health care
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Dankwoord

About the author

Dankwoord

Hier bedank ik iedereen die een professionele of persoonlijke bijdrage heeft geleverd aan het proefschrift. Ik hoop dat dit niet de eerste keer is dat deze mensen horen dat ik ze dankbaar ben, want dan heb ik ze dat tijdens de promotieperiode niet vaak genoeg gezegd. Dit dankwoord geeft mooi weer hoe heel veel grote en kleine waardevolle inspanningen van anderen deze promotie voor mij mogelijk maakten.

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Zonder **het promotieteam** geen promotie; De promotoren dr. Marco H. Blanker, prof. dr. Marjolein Y. Berger en copromotor dr. Henk van der Worp.
Marco, ik wens iedere promovendus een promotor zoals jij toe. Jouw begeleiding was altijd binnen handbereik, van professioneel niveau, richtinggevend zonder te sturen, duidelijk en vriendelijk. Daarnaast neem ik een voorbeeld aan hoe jij je ervaring als huisarts, onderzoeker en epidemioloog combineert en toepast in de verschillende rollen, zonder daarbij oog voor de patiënt te verliezen. Als promotor gaf jij mij de handvaten om me te ontwikkelen tot een zelfstandig onderzoeker, gaf je me de vrijheid om verdieping te zoeken en gaf je nooit een krimp als ik (vaker dan eens) met een nieuw initiatief kwam. Ik heb het promotietraject met veel plezier beleefd en daar heb jij een grote rol in gespeeld.
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About the author

Anne Loohuis was born in Oldenzaal, The Netherlands, on May 12th 1989. She grew up with one younger brother, Wouter.

Secondary school: VWO combined with playing softball at professional level. She followed gymnasium at "Het Twents Carmel College Lyceumstraat" in Oldenzaal from 2001 to 2005. She graduated with VWO at "Het Stedelijk Lyceum Zuid" (2005-2007) where she combined secondary school with playing softball from 2003 to 2007. She played at national level with her team at *Run '71* in Oldenzaal. She joined the national selections <16 years and <18 years and received the silver medal at the European championships in 2004 in Tuchtkova, Russia.

Medicine. She studied Medicine at the University of Groningen from 2007 through 2013. During these years she enjoyed organizing sportive activities at the Medical Faculty Association *Panacea* (2007-2009) and she was a softball coach- and player at the local softball club *Caribe*. Together with 5 other medical interns she started the foundation *Medical Fundraiser Friesland* in 2012, of which she was president in 2012. This foundation organizes a yearly fundraiser for which medical interns, residents and specialists working in the Frisian hospitals and the Frisian province are invited.

Research interest and working experience. Her special interest in scientific research was raised during her last year of her medical study, when she followed her scientific rotation under the supervision of prof. dr. G.H. Koppelman, pediatrician. After receiving her medical degree in 2013, she worked as a resident at the department of Pediatrics at the Medical Center Leeuwarden for one year. During this year she oriented on career paths and decided to become a general practitioner and researcher.

General Practitioner vocational training. Anne started the general practitioner vocational training in January 2015 and combined this with a PhD-traineeship at the department of General Practice and Elderly Medicine at the University Medical Center Groningen. During this time she was also trained as an epidemiologist B at the Epidemiological Society in the Netherlands. During this trajectory, she was member of the scientific curriculum for the GP vocational training, she was board member of the local student representation "LOVAH" (Landelijk Orgaan voor Aspirant Huisartsen) and she participated in projects to improve student participation in the development and evaluation of the curriculum for GP vocational training in Groningen and Zwolle.

The thesis was written under the supervision of prof. dr. Marjolein Y. Berger, dr. Marco H. blanker and dr. Henk van der Worp. She intensively worked together with drs. Nienke J. Wessels, with her focusing on the project evaluation. During this PhD traineeship Anne had a special interest in project management, good clinical practice and research communication engaging the general public.

Currently, Anne is in her last year of GP vocational training, she expects to be a general practitioner in 2022. She then hopes to combine clinical work with research.

She lives with Peter Rosier and together they have two sons, Jens (2018) and Tijn (2020).

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