# Randomized Controlled Non-inferiority Trial of Blended Smoking Cessation Treatment versus Face-to-Face Smoking Cessation Treatment: Comparing Prolonged Abstinence

———————————

A Bachelor Thesis

Presented to

The Faculty of the Department of Behavioural, Management and Social Sciences

University of Twente

———————————

In Partial Fulfilment

of the Requirements for the Degree of

Bachelor of Science

Psychology

———————————

by

Carlotta van Gils

July 3, 2020

First supervisor: Dr. M.E. Pieterse, associate professor

Second supervisor: L. Siemer, PhD candidate.

Total number of words: 7628

## **Abstract**

### **Background**

Online treatment is a recent, emerging development in achieving behavioural change. Web-based components are increasingly added to or blended with traditional face-to-face treatment. In blended treatment, the strengths of one method are expected to compensate for the weaknesses of the other method (van der Vaart et al., 2014). For this reason, blended smoking cessation in considered promising.

### **Aims**

The primary objective of this research is to evaluate the effectiveness of the blended smoking cessation treatment (BSCT) compared to face-to-face treatment(F2F) by measuring prolonged abstinence (i.e. 15 months after the start of treatment, 12 months after the set quit date of treatment) and testing for non-inferiority of BSCT.

### **Setting**

The face-to-face components of both treatments were organised at the outpatient smoking cessation clinic at the hospital Medisch Spectrum Twente. The web-based components could be accessed at home via the Tactus's website of addiction treatment http://www.rokendebaas.nl. The intensity, content, and flexibility were similar for both treatments.

### **Participants**

The participants were patients (at least 18 years old) who were referred by their treating physicians of Medisch Spectrum Twente or by their general practitioners to the outpatient smoking cessation clinic at the hospital in Enschede, Netherlands. The participants all smoked at least one cigarette a day, had access to the internet, and sufficient Dutch reading and writing

skills. Of the 344 participants who started treatment, 177 participants were randomly assigned to F2F and 167 participants were randomly assigned to BSCT. 46 participants (F2F: n=29, BSCT: n=17) finished the 15 months follow-up questionnaire.

## Findings

The non-inferiority analysis showed a significantly lower biochemically validated prolonged abstinence rate for BSCT (1.8%) compared to F2F (9.8%), with a difference of 8% (CI: 2.95 – 13.18; P=0.002) Self-reported abstinence shows similar results, 3% showed prolonged abstinence for BSCT and 11.3% for F2F (difference 8,3% (CI:4.39 – 15.49; P=0.003)).

In regard to adherence, there was no significant difference found between treatments. However, within BSCT there was a significant difference in adherence between the F2F-mode and Web-mode (p=0.001). Of 125 patients, 72% were classified as high adherent to the F2F-mode whereas only 28% was high adherent to Web-mode. Additionally, the majority of patients (89,6%) who followed BSCT were more adherent to the F2F-mode compared to the Web-mode. Furthermore, low adherence in combination with BSCT compared to low adherence in F2F, was not identified as an indicator for quitting smoking (p=0.997), which could also be said for high adherence (p=0.997).

## Conclusion

The non-inferiority analysis was inconclusive. Furthermore, tthere was no interaction effect of BSCT found on adherence and the outcome. However, it is confirmed that the strength of F2F, adherence, is able to compensate for the weakness of BSCT.

## Introduction

Smoking causes severe health issues, such as cardiovascular diseases, cancer, and Chronic Obstructive Pulmonary Disease (COPD) (Aveyard, 2020; CBS, 2017; Christenhusz, 2006; WHO, 2014). It is the main contributor to preventable premature death (Feenstra et al., 2005; Jorenby, 2001; WHO, 2019). The risks and preventability emphasise the importance of smoking cessation, which significantly increases life expectancy (CBS, 2017). Depending on age, and the duration and intensity of smoking, the body can still (partly) recover and therefore reduce the risk of tobacco related diseases (Jorenby, 2017). When already suffering from a disease like COPD, smoking cessation can slow down the development of the disease and improve quality of life  Chavannas et al., 2017; Hagens et al., 2017; Jorenby, 2017).

Although some people manage to quit smoking without professional guidance, higher success rates have been documented amongst people who receive support (Feenstra et al., 2005; Siemer, 2016; Van Aerde, Croes & Willemsen, 2020). The highly addictive nature of smoking and the withdrawal symptoms make it difficult to quit smoking without help or only using self-help methods (Trimbos instituut, 2020; van Aerde, Croes & Willemsen, 2020). Fiore et al. (2008) reports 8,5 % smokers quit smoking without professional support, whereas 27,6 % smokers quit with professional support in combination with medication. The success rate is influenced by social support, psychological factors, intensity of counselling, and the level of self-efficacy (Fiore et al., 2008).

### Blended treatment

Bringing together face-to-face professional guidance and web-based interventions is called blended treatment (Kloek et al., 2017). Online treatment is a recent, emerging development in achieving behavioural change (Kloek et al., 2017). Online interventions are usually offered via a website or an app. In contrast to face-to-face treatment, web-based treatment is easily accessible at any moment and place. However, a strong disadvantage is the lack of adherence (Gerhards et al., 2011), which face-to-face treatment can possibly compensate for (Kelders et al., 2012). In smoking cessation treatment, adherence is usually defined as program attendance (Patterson et al., 2003). Combining the personal guidance of a health professional and the accessibility of online modules is considered a highly promising blend (van der Vaart et al., 2014).

**Previous research on blended treatment**

A growing body of research focuses on blending treatment for mental disorders (Erbe et al., 2017) and chronic somatic disorders (Kloek et al., 2017). Erbe et al. (2017) discuss four different types of blended treatment for mental disorders. These treatments are either mainly internet or face-to-face focused. When face-to-face treatment was the main focus of an intervention, web-based treatment was either used as an addition to face-to-face treatment or replaced some parts of the treatment. Face-to-face treatment was only used as an addition to the internet focused interventions in order to increase adherence. When web-based modules were offered as an additional element, the number of dropouts was reduced (Erbe et al., 2017). Additionally, patients who were addicted to a substance, showed greater restraint. The abstinence rate was greater for these patients.

Out of the six studies in which Erbe et al. (2017) conducted research on replacing face-to-face aspects with online modules, three studies show that time was used 50 to 86% more efficiently, without adversely impacting the effectiveness of the treatments. Kooistra et al (2019) found different results. Due to online feedback, the average time spent per patient by health professionals was similar. Therapists report difficulty adapting to providing online feedback, especially because it is not possible to add nuance with non-verbal behaviour (Mol et al, 2019). Feedback online can come across harsher, as it is more black and white (Mol et al 2019). Perhaps the time spent on giving feedback will be reduced once professionals are adapted to this form of treatment.

The studies compared by Erbe et al. (2017) do not show how effective blended treatment is in relation to face-to-face or internet-based treatments. More recent research by Kooistra et al (2019) does compare the cost and effectiveness of blended versus standard cognitive behavioural therapy for outpatients with depression. Web-based components replaced almost half of the face-to-face sessions, which is on par with this study. Results show great potential for the partial replacement of face-to-face guidance by online treatment as the clinical results are similar. It did not result in reduced effort for the patients and professionals as the online components also took a significant amount of time to finish and give feedback about. This means that it might be beneficial to design efficient web-based components if cost-effectiveness is a goal.

The studies compared by Erbe et al. (2017) also do not indicate the optimal combination of face-to-face and web-based components. A study by Mol et al. (2019) reports views of therapists on blended treatment for patients who suffer from depression. The therapists had different ideas about the ideal ratio of face-to-face and online treatment. Some favoured a 50/50

approach, whereas others favoured an approach where face-to-face was excessively dominant (Mol et al., 2019).

**Blended smoking cessation treatment**

Different methods (e.g. drugs, face-to-face, web-based) have been developed to help people quit smoking (Feenstra et al., 2005). Multiple methods have been proven to be effective, but all come with advantages and disadvantages.

The traditional intensive face-to-face cognitive behaviour treatment has proven to be effective, especially in combination with drugs (e.g. nicotine patch, nicotine gum, antidepressants) (Chavannas et al., 2017; Coleman, 2004). This combined approach can more than double the success rate compared to no treatment (WHO, 2014). In general, a higher intensity of face-to-face treatment will result in higher abstinence rates (Fiore et al., 2008). Intensity can relate to the duration of treatment sessions, the number of sessions, or both. The treatment is expensive due to the intensity, and therefore can be less accessible (Fiore et al., 2008). Additionally, smokers might not be interested in an intensive treatment at all. Patients are required to travel to the treatment facility during office hours, which takes time and might cost money (Siemer et al., 2106). It could be costly to travel and take time of work. Furthermore, therapist drift is a known effect of face-to-face therapy (Mansson et al., 2013). The focus of the treatment can shift from taking action to talking due to cognitive distortions, emotional responses and the use of safety behaviour (Waller, 2009). In turn, face-to-face contact does increase the capacity to show empathy and form a close relationship of mutual understanding (Fitzpatrick, 2018).

Due to the high availability and accessibility of the internet, web-based smoking cessation treatment is an attractive and logical development (Civljak et al., 2013; Fitzpatrick et al., 2018; Marsh & Rajaram, 2019; Siemer et al., 2018). It is thought to be attractive for multiple reasons. First of all, the costs per user are low (Civljak et al., 2013). In the Netherlands, the cost of professional help to quit smoking is covered by insurance (Kuijper, 2019). Since January 2020, the deductible has been abolished to remove all cost barriers to call on professional help for smoking cessation (Kuijper, 2019). Low costs increase the likelihood that the insurance companies will keep offering the treatment, as they operate in a competitive environment (Christenhusz, 2006; Leu et al., 2009). Therefore, low costs ensure accessibility.

Secondly, web-based treatment is attractive because of its flexibility. It might be more fitting to a patient, as patients can do the treatment whenever they see fit and in their own preferred environment (Civljak et al., 2013; Fitzpatrick et al., 2018). This is convenient, and

most likely also results in lower personal costs in terms of time and effort. Further, health professionals can respond to clients at a time that fits best with their schedule and less face-to-face sessions are provided (Mol et al., 2019). This increases efficiency and saves time. The saved time can be used to help more smokers, also increasing accessibility (Mol et al., 2019). However, as giving feedback online can be challenging, it could result in additional time spent depending on the health care professional's experience with giving online feedback (Kooistra, 2019).

Thirdly, web-based components can replace meetings missed by patients, which has a positive effect on engagement (Siemer et al., 2016). On the contrary, the largest offset of online treatment is the lack of adherence owing to limited face-to-face contact.

Lastly, web-based components can counterbalance for therapist drift. A reduction of therapist drift was noticed by therapists when incorporating web-based elements (Mol et al., 2019). The pre-set structure of web-based modules helps to emphasize the work that patients have to put in for the treatment to be successful, which reduces therapist drift (Mol et al., 2019). Online assignments make it easier to stay on track (Mol et al., 2019) and encourage patients to take on an active role (Fitzpatrick et al., 2019; van der Vaart et al., 2014).

Thus, web-based treatment is easily accessible, stimulates efficient time use by patients and counsellors and therefore web-based treatment helps to reach more patients (Siemer et al., 2016). In addition, the possibility of replacing face-to-face meetings with web-based sessions could increase engagement. In turn, the lack of personal contact has shown to lead to a decrease in adherence (Siemer et al., 2016). Offering face-to-face treatment could improve the adherence of patients (Kloek et al., 2017) and compensate for the limited capacity to show empathy online. The idea is that the strengths of one method compensates for the weaknesses of the other method. For these reasons, blended treatment is expected to be effective, possibly cost-efficient and may lead to greater user satisfaction.

**Objectives**

The primary objective of this research is to evaluate the effectiveness of the blended smoking cessation treatment (BSCT) compared to the face-to-face treatment (F2F) by reporting prolonged abstinence rates and testing for non-inferiority of BSCT. Prolonged abstinence measurements were performed 15 months after the start of the treatment, which is 12 months after the expected stop date, and 9 months after the end of the treatment. To the best of our knowledge, no study has compared prolonged abstinence rates for blended smoking cessation treatment (BSCT) and face-to-face treatment (F2F). As the strengths of one method are

expected to compensate for the weaknesses of the other method , blended smoking cessation is considered promising (van der Vaart et al., 2014).

Medisch Spectrum Twente (MST) offers a personalized face-to-face treatment to patients who are referred to the outpatient clinic by a physician or GP. This tested method has proven to be effective  (Christenhuz, 2006). As this form of treatment also has a few downsides (e.g. high costs), it is considered useful to research if this could be offered differently. Lowering the treatment costs would increase the chance of smoking cessation covered by insurance (Christenhusz, 2006; Leu et al., 2009).

Identical content is offered for both BSCT and F2F in order to make a reliable comparison. Both treatments consist of 10 sessions spread over 6 months. BSCT offers 5 out of 10 sessions online. A non-inferior analysis will demonstrate whether BSCT is at least not worse than F2F by the predetermined margin of 5%.   Secondary effects (user satisfaction and cost-effectiveness) will be a sufficient motivator to implement blended treatment, even if the success rate remains more or less the same. These secondary effects will be evaluated in other connected studies. Furthermore, it would be beneficial to offer an additional treatment option, so there is more variety. Meaning that patients would have more options to personalize treatment.

A secondary objective is to compare the adherence of both treatments, and adherence within BSCT. The chance to relapse is lower when adherence is high and higher adherence is associated with higher smoking cessation rates (Patterson et al, 2003) and treatment acceptability (Sabate & Staff, 2013). Furthermore, whether BSCT has an interaction effect on adherence and smoking cessation is investigated.

## Methods/Design

This section is based on the protocol article by Siemer et al. (2016).

### Participants

The participants were patients who were referred by their treating physicians of Medisch Spectrum Twente or by their general practitioners to the outpatient smoking cessation clinic at the hospital in Enschede, Netherlands. These patients signed up for smoking cessation treatment at the outpatient clinic and choose to participate in this study voluntarily. All patients (1) were at least 18 years old, (2) smoked at least one cigarette a day at the start of the study, (3) had access to and know how to use email and websites, and (4) had a sufficient level of Dutch

reading and writing skills. Of the 344 participants who started treatment, 177 participants were randomly assigned to F2F and 167 participants were randomly assigned to BSCT. Randomization was executed with the use of QMinim Online Minimazation (http://qminim.sourceforge.net/) at individual level (1:1). The participants were arranged based on level of internet skills, level of nicotine dependence; and the preferred quitting strategy of a patient. 46 participants completed the 15-month follow-up questionnaire. These participants were either following F2F (n=29) or BSCT (n= 17). All patients signed an informed consent beforehand. Both patients and researchers needed to know who participated in which treatment. Therefore, this study was an open label study.

**Study intervention**

Both F2F and BSCT were accommodated by the Outpatient Smoking Cessation Clinic (SRP). The SRP is part of the Department of Pulmonary Medicine of MST. All sessions of F2F have taken place at the SRP. As mentioned before, BSCT consists of five face-to-face sessions and five web-based sessions. The face-to-face sessions also took place at SRP, whereas the web-based sessions were accessed at home via Tactus's website for addiction treatment http://www.rokendebaas.nl. Experts and counsellors were involved in designing the most appropriate mix of all the components. The web-based sessions were considered a suitable delivery method for the content, while still maintaining the intensity of the treatment. As high intensity is commonly an indicator for success, it was deemed important to match this for BSCT (Fiore et al., 2008). The distribution, main features, and form of delivery of BSCT can be found in table 1.

**Table 1**

*Order, timing, main features, and mode of delivery of blended smoking cessation treatment. Quoted from Siemer et al. (2016).*

| Session | Week | Main features | Mode of delivery |
| --- | --- | --- | --- |

| 1 | 1 | Goal setting, prompt smoking diary, measure CO* | Face-to-face |
|---|---|---|---|
| 2 | 3 | Measures for self-control | Web-based |
| 3 | 5 | Dealing with withdrawal | Face-to-face |
| 4 | 7 | Breaking habits | Web-based |
| 5 | 9 | Dealing with triggers | Face-to-face |
| 6 | 11 | Food for thought | Web-based |
| 7 | 14 | Think differently, measure CO | Face-to-face |
| 8 | 18 | Do differently | Web-based |
| 9 | 22 | Action plan, measure CO | Face-to-face |
| 10 | 26 | Closure | Web-based |

*CO = carbon monoxide

As F2F is personalized to the patients' needs and therefore offers flexibility in quitting strategies, the same was offered for BSCT. At the start of the treatment, patients could choose between three quitting strategies: (1) Stop at once, (2) gradual change, and (3) scheduled reduced smoking. A detailed description of the strategies can be found in table 2. Recent research favours quitting smoking abruptly over gradual smoking cessation (Wilson & Sherman, 2016), but all strategies are offered for BSCT to allow for comparability with F2F.

**Table 2**

*Quitting strategies*

| Quitting strategies | Steps |
|---|---|
| Stop at once | 1. Set a quit date<br>2. Make a preparation plan<br>3. Stop abruptly on the selected quit date |

| Gradual change | 1. | Identify daily activities, situations and contexts in which smoking is habitual. Examples are: drinking beer/coffee, reading newspaper, talking on the phone, walking to the shop. |
| | 2. | Stop smoking during these activities, situations and contexts step by step |
| | 3. | Set a quit date |
| Scheduled reduced smoking | 1. | Gradually decrease number of cigarettes at regular intervals (100% $\rightarrow$ 75% $\rightarrow$ 50%) |
| | 2. | Continue this process until ready to quit |

The preferred quitting strategy only marginally affect the content of the actual treatment. The number, order and effective components are identical. Both BSCT and F2F offered ten sessions with similar content. These sessions were spread over 6 months and the intensity gradually diminished over time. The first six sessions had approximately two weeks between them, while the last three sessions had four weeks in between each session. The content may have been slightly different in terms of timing of goal-setting due to the preferred quitting strategy.

With regard to comparability, BSCT, just as F2F, contained counsellor-dependent and counsellor-independent components. The greatest difference was the asynchronous communication of BSCT. However, both treatments allowed for interactive communication between counsellor and patient. Furthermore, the counsellor-independent components were offered online for BSCT, whereas these components were provided in a paper manual to use at home for F2F. For both treatments, these components were meant to be completed by the patients on their own and in their own time. Thus, the intensity and content were similar. However, BSCT has an additional benefit. The content of counsellor-dependent sessions can also be viewed afterwards, as messages are saved online.

The similarity in content is also supported by covering most reliable behaviour change techniques that aim at supporting individuals who want to quit smoking for both F2F and BSCT (Michie et al., 2011). These behaviour change techniques are associated with a higher quit rate (West et al., 2010). The distribution of behaviour change techniques can be found in appendix 1.

**Measurements**

The 15 measurements were done after 15 months after the start of the treatment, which is 12 months after the expected stop date, and 9 months after the end of the treatment. The data recorded at baseline and after 15 months are displayed in table 3. Additionally, the following demographical data was collected: sex, age, nationality, cultural background, marital, status, children, housing, education, source of income, and main activity.

**Table 3**

*Measurements baseline & 15 months*

| Variables | Baseline measurements | 15 month measurements |
|---|---|---|
| **Primary outcome** | | |
| Cotinine level | | X |
| **Secondary outcomes** | | |
| Nicotine dependence (Fagerström) | X | |
| MAP-HSS + smoking related complaints of smokers | X | X |
| Depression, anxiety and stress (DASS21) | X | X |
| Quality of Life (Euroqol 5D) | X | |
| Smoking status | X | |
| Adherence | | X |
| Costs | | X |
| **Baseline predictors of treatment effect** | | |
| Internet Skills | X | |
| Readiness to change | X | |
| Attitude | X | |
| Social Influence | X | |
| Self-Efficacy | X | |
| Alcohol/substance (mis)use | X | |
| **Descriptive variables** | | |
| Patient characteristics and medical history | X | |

| | | |
|---|---|---|
| Smoking history | X | |
| Stop Smoking History | X | |
| **Other information of interest** | | |
| Evaluation of treatment | | X |
| Exhaled carbon monoxide (CO) level | X | X |

## Instruments

### Primary outcome

*Cotinine level*

The self-reported prolonged abstinence is biochemically validated by measuring cotinine level. It is considered a reliable method that is capable of sensitive measurements and can therefore also identify passive smokers (Sharma et al., 2019). A 0,5-1 ml salivary sample was collected only from patients who reported quitting smoking. Patients who reported abstinence were asked to chew on a cotton swab for 60 seconds to stimulate salvation. Salivettes were used to store the swabs to ensure high quality samples (Sarstedt AG & Co., Nümbrecht, Germany). The patients were supervised during this process. All the saliva specimens were frozen until the quality could be checked at the laboratory. When the saliva was assayed, a gas chromatography was used to determine the cotinine level. The samples were taken approximately 3 months after the start of the study, depending on the self-selected stop date, and at the 15 months follow-up. A salivary cotinine level lower than 20 ng/ml indicated prolonged abstinence. Patients with higher cotinine levels were categorized as smokers. Patients who did not report abstinence and patients who did not participate in follow-ups were regarded as smokers.

*Exhaled carbon monoxide (CO) level*

Exhaled carbon monoxide (CO) measurements were used when cotinine measurements were missing. The CO measurements were already part of the regular treatment and therefore relatively easy to include. After approximately 24 hours, a smokers CO level will be back to a non-smokers level, so this test does not identify passive smokers (coVita, 2010) and was used as a back-up. Additionally, it presents the opportunity to research differences in measurement methods.

The CO cut-off level is 5 ppm, so patients who have a ppm of 5 or higher were regarded as smokers. The breath of patients was tested with a portable CO monitor, called piCo Smokerlyzer (Bedfont Instruments: Kent, UK).

**Secondary outcomes**

*Adherence*

Adherence was measured by examining the time spent (in minutes) on treatment versus the initial time set for each treatment. Both treatments aimed for a total duration of 230 minutes. For BSCT, 130 minutes were scheduled for face-to-face (F2F-mode) meetings and 100 minutes for the web-based (Web-mode) components. All percentages equal to and above the median split 106,5%) were classified as high adherence and below 106,5% as low adherence. 280 participants were available for the adherence analysis.

**Other information of interest**

*Dropout in intention to treat*

Drop-out rates influence the intention-to-treat results, as dropouts are classified as smokers. Everyone who did not complete the 15 months questionnaire was seen as a dropout. This could possibly results in a bias when there is a difference between both treatment groups.

**Non-inferiority margin**

Based on previous studies within MST and Tactus on smoking cessation treatment, it was expected that 10% of smokers would be abstinent after 15 months from that start of the study. We had foreseen that BSCT would have an abstinence rate of 15% due to the presumed benefits of the blended treatment.

BSCT was regarded as non-inferior, when BSCT was not worse than F2F by 5 percentage points. The margin of 5% was determined on the following reasoning:

(1) Even if participants only engage in the face-to-face components of BSCT, they still follow 50% of the treatment, therefore 50% of the abstinence rate is expected.

(2) When COPD patients received no counselling or pharmacotherapy, only 1.4% validated prolonged abstinence was reported (Hoogendoorn et al., 2010). With minimal counselling (less

than 90 minutes in total) the abstinence rate was 2.4% (Hoogendoorn et al., 2010). Therefore, BSCT will be regarded superior to these methods when applying the 5% margin.

(3) The expected benefits of BSCT are assumed to preponderate over the loss in effectiveness, preferring BSCT over F2F.

**Data analysis**

A non-inferiority analysis was performed to measure prolonged abstinence, as we expected that BSCT was at least non-inferior to F2F. As recommended, the data was analysed based on the intention-to-treat principle (n=344) (Hahn, 2012; Macaya et al., 2017). Additionally, the non-inferiority analysis was also performed on a per-protocol sample (Hahn, 2012; Macaya et al., 2017). Interpretations were based on biochemically validated prolonged abstinence and self-reported abstinence. To allow for future comparisons, self-reported point prevalence and self-reported continuous abstinence were also reported.

Descriptive statistics were used to report the quit rates per treatment group. In order to test for non-inferiority, the difference between the abstinence rates and corresponding confidence intervals were calculated. These results were compared to the previously defined non-inferiority margin of 5%. Additionally, the Pearson chi-square was used to test for significance.

Furthermore, a logistic regression was performed to calculate the odd ratio (OR). In this study, the OR represented the odds of smoking cessation when following BSCT, compared to F2F. The 95% CI of the OR indicated how certain we are about the relative odds (Szumilas, 2010). To identify possible baseline confounders, the 33 baseline characteristics were tested for significance difference between groups. To determine significance difference for continuous variables independent T-tests were performed for normally distributed variables and Mann-Whitney-U tests were run for variables that did not follow normal distribution. Categorical variables were tested for significance with a Pearson chi-square or Fisher's exact test.

In order to explain for possible difference in the treatment outcomes, a Pearson Chi-square was performed to test if there was a difference in adherence between BSCT and F2F. Adherence within BSCT was also reported to be able analyse the adherence to the Web-mode and F2F-mode. Additionally, a logistic regression was used to test for an interaction effect

between adherence and treatment on smoking cessation. Descriptive statistics were used to report the distribution of the outcomes.

All categorical variables were reported as numbers together with the relative percentages.

All analyses, except for the confidence intervals, were performed with SPSS 26. The confidence intervals were calculate using Vassarstat's web tool for "The Confidence Interval For The Difference Between Two Independent Proportions" at http://vassarstats.net/prop2_ind.html.

## Results

### Effectiveness

Table 4 shows the results for effectiveness measurements 15 months after treatment. 21 cotinine samples and 31 CO samples available for the 15 months results. The non-inferiority analysis showed a significantly lower biochemically validated prolonged abstinence rate for BSCT (1.8%) compared to F2F (9.8%), with a difference of 8% (CI: 2.95 – 13.18; p=0.002) Self-reported abstinence showed similar results, 3% show prolonged abstinence for BSCT and 11.3% for F2F (difference 8,3% (CI:4.39 – 15.49; p=0.003)).

**Table 4**

*Treatment effects on number of participants at 15 months after treatment*

|  | Number of abstinent participants in BSCT (%) | Number of abstinent participants in F2F (%) | Risk difference (95% CI) | Group difference (Pearson Chi Square) |
|---|---|---|---|---|
| **Intention-to-treat analysis 15 months** |  |  |  |  |
|  | 3/167 (1.8%) | 17/177 (9.8%) | 8% (2.95 – 13.18) | 0.002 |

| | | | | |
|---|---|---|---|---|
| Biochemically validated (Cotinine and CO) abstinence | | | | |
| Self-reported abstinence | 5/167 (3%) | 20/177 (11.3%) | 8.3% (2.29 – 14.07) | 0.003 |
| Self-reported point prevalence abstinence | 4/167 (2.4%) | 18/177 (10.2%) | 7.8% (2.27 – 13.3) | 0.003 |
| Self-reported continuous abstinence | 3/167 1.8% | 13/177 7.3% | 5.5% (1.05 – 10.5) | 0.015 |
| **Per-protocol analysis 15 months** | | | | |
| Biochemically validated (Cotinine and CO) abstinence | 3/17 (17.6%) | 17/29 (58.6%) | 41% (11.54 – 60.54) | 0.007 |
| Self-reported abstinence | 5/17 (29.4%) | 20/29 (69%) | 39.6% (9.66 – 60.76) | 0.009 |
| Self-reported point prevalence abstinence | 4/17 (23.5%) | 18/17 (62%) | 38.5% (8.71 – 59.22) | 0.008 |
| Self-reported continuous abstinence | 3/17 (17.6%) | 13/29 (44.8%) | 27.2% (-1.39 – 48.2) | 0.051 |

If BSCT is non-inferior to F2F, we would expect that the non-inferiority margin (NI margin) is excluded from the CI of the risk difference (Althunian et al., 2017; Macaya et al., 2017). Then, the upper bound of the CI should be below the margin of non-inferiority. If the upper CI is above the non-inferiority margin, BSCT would be inferior to F2F (Macaya et al., 2017). When the lower CI is lower than 0 and the upper CI above the NI margin, it indicates insignificance and therefore, the result would be inconclusive (Macaya et al., 2017). To prove inferiority, both CI's should also be excluded from the NI margin, but instead the lower bound of the CI should be above the margin.

The results in table 4 exhibit that the upper bound of CI is above the non-inferiority margin (13.18 > 5) for biochemically validated abstinence. The lower bound of CI is within the NI margin. Similar can be concluded for self-reported abstinence (14.07 > 5) Therefore it can be concluded that non-inferiority of BSCT compared to F2F could not be shown. The results strongly point towards BSCT being inferior to F2F, however it could not be proven indefinitely. These results are illustrated in figure 1.
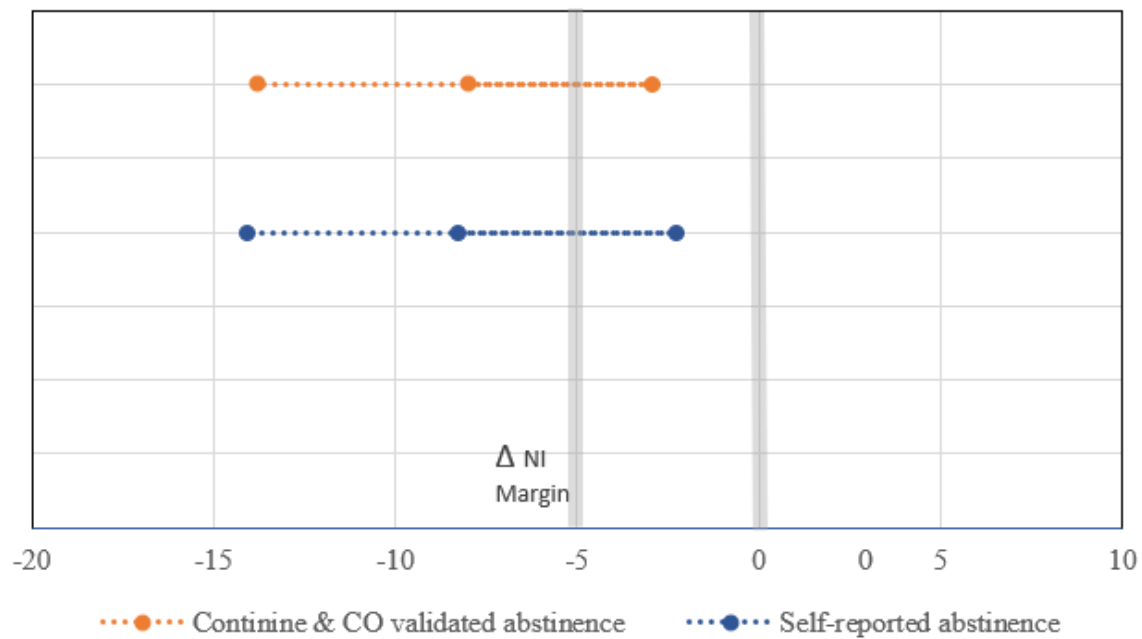


**Figure 1**

*Validated and self-reported abstinence*

Additionally, the odd ratio (OR) was calculated for biochemically validated prolonged abstinence rate. There was no significant difference between groups observed for baseline characteristics. The OR (5.8; CI: 1.66 – 20.42) indicates that the likelihood of achieving long term abstinence is 5.8 higher for F2F than for BSCT. As the baseline characteristics were (almost) evenly divided over each group, the OR was not corrected for baseline confounders.

**Adherence between treatments**

The actual time spent per treatment was documented for 280 participants. Table 5 illustrates the distribution of low and high adherence among BSCT and F2F. From the Pearson chi square (p=0.660) it can be concluded that there is no significance difference between treatments.

**Table 5**

*Distribution of low and high adherence among BSCT and F2F*

|  | BSCT (%) | F2F (%) | Total (%) |
|---|---|---|---|
| Low adherence (%) | 79 (28.2%) | 76 (27.1%) | 155 (55.4%) |
| High adherence (%) | 60 (21.4%) | 65 (23.2%) | 125 (44.6%) |
| Total (%) | 139 (49.6%) | 141 (50.3%) | 280 (100%) |

Nonetheless, comparing F2F treatment to the F2F-mode of BSCT, the median was higher for F2F in BSCT (106.5% vs 150%). The dissimilarity is remarkable as it indicates an imbalance within BSCT. This observation was the motivator to dive into the difference within BSCT.

**Adherence within BSCT**

As expected based on the difference between the medians of F2F and the F2F-mode of BSCT, a strong imbalance within BSCT was noticed. Of 125 patients, 72% were classified as high adherent to the F2F-mode whereas only 28% was high adherent to Web-mode, indicating significant difference in adherence between the F2F-mode and Web-mode (p=0.001). Table 6 shows the distribution of low and high adherence for BSCT.

**Table 6**

*Distribution of low and high adherence within BSCT*

|  | Low adherence F2F-mode (%) | High adherence F2F-mode (%) | Total (%) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Low adherence Web-mode (%) | 33 (26,4%) | 57 (45,6%) | 90 (72%) |
| High adherence Web-mode (%) | 2 (1.6%) | 33 (26,4% | 35 (28%) |
| Total (%) | 35 (28%) | 90 (72%) | 125 (100%) |

The imbalance within BSCT became more apparent when examining the number of cases where adherence was higher for the F2F-mode compared to Web-mode. The majority of patients (89,6%) who followed BSCT were relatively more adherent to the F2F-mode compared to the Web-mode.

**Effect of adherence on treatment**

The effect of adherence on the outcome (smoking cessation) is strong. The odds are 8.3 (95% CI: 2.37 – 29.053) times higher to quit smoking for high adherence compared to low adherence. The distribution of the outcomes and adherence per treatment can be seen in table 7.

When BSCT was introduced as an interactor, it did not show significant results. Low adherence in combination with BSCT compared to low adherence in F2F, was not identified as an indicator for quitting smoking (p=0.997), which can also be said for high adherence (p=0.997). Thus, no interaction term was identified for BSCT compared to F2F.

The Nagelkerke R Square changed from 0.249 to 0.257 when the interaction term was added, meaning that slightly more of the variance in the data was explained by the model.

**Table 7**

*Distribution of high and low adherence for both treatment outcomes*

| | Abstinent | Non-abstinent | Total |
|---|---|---|---|
| **BSCT** | | | |
| Low adherence | 0 | 78 | 78 |
| High adherence | 3 | 72 | 76 |
| Total | 3 | 150 | 153 |

| F2F | | | |
|---|---|---|---|
| Low adherence | 3 | 57 | 60 |
| High adherence | 17 | 48 | 65 |
| Total | 20 | 105 | 125 |

**Dropout**

298 out of 344 (86.6%) participants were considered as dropouts. The distribution is shown in table 8. BSCT had a little more than half (50.3%) of the dropouts, even though the group was smaller (n=167). However, the difference of dropouts between treatment was nonsignificant according to Pearson chi square (p=0.09).

**Table 8**

*Distribution of dropouts among BSCT and F2F.*

| | | Number of participants completing the 15-months follow-up (% of total) | Number of participants not completing the 15-months follow-up (% total) | Total |
|---|---|---|---|---|
| Treatment | BSCT | 17 (4.9%) | 150 (43.6%) | 167 (48.5%) |
| | F2F | 29 (8.4%) | 148 (43%) | 177 (51.4%) |
| Total | | 46 (13.4%) | 298 (86.6%) | 344 (100%) |

**Discussion**

**Main findings**

This non-inferiority analysis was a randomised controlled trial investigating effectiveness by comparing prolonged abstinence between blended smoking cessation treatment (BSCT) and face-to-face treatment (F2F). BSCT was designed to match the characteristic (intensity, behaviour change techniques, and flexibility) of F2F. The non-inferiority analysis showed that non-inferiority, as well as inferiority, could not be proven. Thus, results were inconclusive.

Based on these results, we cannot write off BSCT, but we cannot ignore that the results lean more towards inferiority. This is supported by the found odd ratio of 5.8, which indicates that the odds to quit smoking are significantly better for F2F. A small remark is that there is a high level of uncertainty about the exact odds. However, there it is clear that there is a significant difference between treatments in favour of F2F. Also, if we only compare the abstinence rate, it can be concluded that BSCT did significantly worse in terms of effectiveness.

The validated abstinence rate of F2F (9.8%) was expected based on previous research by Christenhusz (2006). On the contrary, abstinence rates for BSCT were lower than expected. However, the results should be interpreted with caution, as there is some uncertainty about the outcome. The baseline characteristics and adherence, are not seen out as possible explanation for the difference in outcome.

As adherence is seen as an important indicator for success and associated with treatment acceptability (Sabate & Staff, 2013), it was further investigated. Even though there was no significant difference in adherence between treatments, within BSCT the difference was large. Within BSCT, the Web-mode scored 61.1% lower on adherence than F2F-mode. Additionally, when we compare relative difference between the adherence of the F2F-mode of BSCT compared to face-to-face treatment, participants were 29% more adherent to the F2F-mode of BSCT opposed to the face-to-face sessions of F2F. It suggests that participants who followed BSCT, made more use of the face-to-face time they had with a counsellor and/or requested extra time.

Thus, results on adherence imply that face-to-face sessions are able to compensate for the low adherence in BSCT. This confirms that the strength of face-to-face treatment, namely adherence, is able to compensate for the related disadvantage of online treatment under the condition that there is room for personal differences. These personal differences refer to preferred proportion of face-to-face and web-based sessions. Even though no exact numbers are known, extra sessions have been requested by patients. The flexibility in requesting extra F2F time was not part of the study design, so counsellors deviated from the protocol. Treatment integrity is compromised when not following protocol (Fryling, Wallace, & Yassine, 2012; Mocher & Prinz, 1991). It possibly increased adherence in BSCT by allowing for more face-to-face sessions. On the other hand, if counsellors preferred face-to-face over online treatment, it is likely they steered more in the direction of face-to-face sessions, undermining BSCT and therefore its effectiveness. All quitters in BSCT were high adherent to treatment. However, none of the quitters compensated for low adherence in  the Web-mode with high adherence in

the F2F-mode. These 3 quitters were high adherent in both modes and relatively spend the same time on each of the two modes. It is therefore likely that promoting both modes had a positive effect on the outcome, and therefore, the deviation from the protocol could have had a negative effect on the abstinence rate of BSCT, possibly explaining (part of) the disappointing results. Because of the limited available data and limited knowledge on fidelity in BSCT, uncertainty remains on this topic.

The limited data of quitters also had an effect on the visibility of the importance of adherence. It can be concluded that adherence is important for both treatment groups. However, it is more visible for F2F, as there was more data available, especially for quitters.

To be able to fully interpret the results and give adequate advice, the selected non-inferiority margin is also assessed. According to the CI of the risk difference, it is possible that BSCT still falls within the predefined 5% margin, therefore the results are inconclusive. However, there is no doubt that BSCT is less effective than F2F. The selected margin is based on subjective reasoning and is therefore subjected to statistical risk of false conclusions (Althunian et al., 2017). The question arises if the 5% margin, meaning a drop of 50% in effectiveness, is really acceptable. Part of this margin was based on the worst case scenario that no one would adhere to the web-based components of BSCT. This scenario could not be considered acceptable, as then the blended aspect of the treatment would be non-existent. There would be no use in implementing BSCT of this would be the case and the margin is therefore not considered as an appropriate cut off point. Additionally, with the knowledge that user satisfaction is similar for both treatments (Siemer, Ben Allouch, et al., 2020), it can be said that at least one expected benefit for BSCT does not compensate for the loss in effectiveness. A lower non-inferiority is considered more appropriate. A lower margin of 2.5% would have resulted in inferiority of BSCT compared to F2F for the validated prolonged abstinence.

Taking all the above arguments into account, it would not be advised to implement BSCT based on the available data.

**Comparison to other studies**

The abstinence rates that were found in this study were lower than found among general population (Fiore et al., 2008). However, we have to keep in mind that the population of this study had more (severe) health issues. In this study, a few patients actually reported they started

smoking again, as they received bad news about their health, or because their health decreased. Research by Shiffman (2005) on dynamic influences on smoking relapse shows that acute negative circumstances (such as receiving bad news), perceived stress and emotional states form a great risk for relapse. Health issues affect a person's wellbeing including psychological functioning and affective states (U.K. Department of Health, 2014). Thus, it makes sense that abstinence rate is lower for this group of people.

As this is one of the first studies to compare effectiveness of blended smoking cessation to face-to-face treatment, the options to compare our findings with similar research is limited. More research is done on blended treatment for CBT targeting mental disorders. Recent research of Kooistra et al (2019) compares the cost-effectiveness and effectiveness of blended CBT to traditional CBT (face-to-face) treatment in patients with depression, which showed similar clinical results for both blended and traditional treatment. Analysing the characteristics of both this study and the study of Kooistra et al. (2019), there is not a clear explanation for the contradicting results. However, it is remarkable that the analysis of Kooistra et al. (2019) was performed after 30 weeks, while some people were still receiving treatment after those 30 weeks. This is a strong bias in favour of blended CBT. Future research could account for possible explanations of the contradictory results.

**Limitations**

Limited available data (n=46) is seen as a major limitation of this study. Covid-19 intensified this problem, as the support of non-essential research was (temporarily) cancelled at Medisch Spectrum Twente. Therefore, the paper questionnaires were not available. Also, it was no possible to approach participants by phone to ask for participation in follow-up cotinine measurements and questionnaires. Because of the small sample, possibly more patients were classified as smokers when applying intention to treat principle. CO and cotinine measurements may had a relatively larger effect. However, the effect of missing data due to Covid-19 seems to only marginally affect the outcome, as the intermediate 6-month results were already not promising (Siemer, Pieterse, et al., 2020). Subsequently, the chance of relapsing after 6 months is still relatively high (+/-50%) (Trimbos instituut, 2016). This chance drops below 10% after 12 months from the stop date (Trimbos instituut, 2016). Therefore, it was expected that the results would be worse for the 15 month analysis (12 month after stop date) compared to the 6 months analysis.

The limited data available might have also made dropout appear worse than it is. Intensified drop-out rates are known effect seen in a intention-to-treat analysis. This would only be a problem when both groups are not equally effected. Officially no significance difference (p=0.09) was found between treatments. Nevertheless, the Pearson Chi Square indicates inequality between treatments. BSCT was effected more by dropouts than F2F. However, if we take the ratio of quitters in F2F, and apply it to BSCT, we would expect almost 10 quitters for BSCT. It is not considered likely that this difference of 7 could be completely accounted for by the effect of drop-out.

The way adherence was calculated is also seen as a limitation. Adherence was defined by the time spent on treatment divided by the initial time. Based on previous research on a range of smoking cessation treatments (Afzal, Pogge, & Boomershine, 2017; Ben Taleb et al., 2015; Karadogan et al., 2018; Ranjani et al., 2019), it is not likely that adherence was, in most cases, above 100%. It does show that the time needed for treatment was underestimated. Furthermore, time spent on treatment does not give us insights in completed assignments. However, the interpretation of adherence is still considered useful as the relative difference is compared.


**Recommendation for future research**

First of all, it would be recommended to focus on reducing drop-out, as limited data caused uncertainty in the outcomes. In this study, we intended to reduce drop-out by calling patients to fill in the follow-up questionnaire and come in for cotinine measurements. This was not possible due to corona and the inability to access privacy sensitive data. Other reasons for drop-out first need to be determined for them to be targeted.

Additionally, even though more patients were more adherent to the F2F-mode of BSCT, 11% of participants showed greater adherence to Web-mode compared to the F2F-mode. Thus, it is likely that people have different preferences. Qualitative research could identify the reasons why relatively more time was spend on the web-based components, as well why most people did not adhere to these web-based sessions. This information could serve as input for more personalized blended treatment. It is not likely that the 50-50 ratio works well for everyone, as people all have different needs and wishes. An online program should be flexible enough to adapt to these different needs (van der Vaart et al., 2014). Counsellors highlight the importance of taking into account individual differences and characteristics to choose for blended treatment (van der Vaart et al., 2014). For example, face-to-face time is recommended for support in

practical difficulties and feelings (van der Vaart et al., 2014). Therefore, it might be beneficial to adopt a different ratio for patients in need of emotional support. It recommended that more research is done on the ideal ratio of blended care. It is not expected that one size fits all, but a few sizes fits most approach would be considered useful.

An advise would be to apply person-centred care with shared decision-making (Adams & Grieder, 2014). To help assign patients to the most appropriate treatment, characteristics should be identified that fit either web-based and or face-to-face treatment. It should be taken into account that this personalized care does not eliminate the possible cost-efficient character of BSCT. In order to save time, and therefore money, a standardized questionnaire could be designed. This would be a onetime investment.

Additional recommendation for future research are finding out more about the contradicting results of both blended treatments. Is there a difference between smoking cessation patients and depressive patients? Or are there certain key characteristic (high intensity vs low intensity, e-mail vs texts, smartphone vs computer) that influence the chances of success?

**Conclusion**

This study provides insights in the effectiveness of blended smoking cessation treatment and the role of adherence. Even though the non-inferiority analysis showed inconclusive results, it is clear BSCT is significantly worse than F2F considering effectiveness. Therefore, based on the available data, it is not recommended to implement BSCT as it is. However, it is considered promising that the F2F strength, adherence, is able to compensate for the weakness of BSCT. It is advised to direct future research towards individual differences and the flexibility of the 50-50 ratio of BSCT to be able to make appropriate adjustments. Additionally, it would be recommended to focus on reducing drop-out to avoid inconclusive results, and to focus on the existence and effect of treatment fidelity in BSCT.

the counsellors and other researchers involved, I appreciate the work that has been done to provide me with an interesting research subject.

# References

Adams, N., Grieder, D. (2013). *Treatment Planning for Person-Centered Care.* Academic Press. https://doi.org/10.1016/C2011-0-06989-2

Afzal Z., Pogge, E., Boomershine, V. (2017). Evaluation of pharmacist and nurse practiotioner smoking cessation program. *J Pharm Pract, 30*(4), 406-411. doi 10.1177/0897190016659221

Althunian, T.A., de Boer, A., Groenwold, R.H.H., Klungel, A.H. (2017). Defining the noninferiority margin and analysing noninferiority: An overview. *British Journal of Clinical Pharmacology, 83*(8). https://doi.org/10.1111/bcp.13280

Aveyard, P. (2020). Smoking cessation. In Oxford Textbook of Medicine. doi 10.1093/med/9780198746690.003.0642

Ben Taleb, Z., Ward, K.D., Asfar, T., Bahelah, R., Maziak, W. (2015). Predictors of adherence to pharmacological and behavioral treatment in a cessation trial among smokers in Aleppo, Syria. *Drug Alcohol Depend*, *153*, 167-172. doi 10.1016/j.drugalcdep.2015.05.038

CBS (2009). Richtlijn behandeling van tabaksverslaving, herziening 2009 [Guidelines for treating tobacco addiction]. Utrecht: Centraal BegeleidingsOrgaan.

CBS (2017). *Heavy smokers cut their lifespan by 13 years on average*. Retrieved February 19, 2020 from https://www.cbs.nl/en-gb/news/2017/37/heavy-smokers-cut-their-lifespan-by-13-years-on-average

Chavannas, N.H., Meijer, E., Wind, L., van de Graaf, R.C., Rietbergen, C., & Croes, E.A. (2017). Herziene richtlijn 'Behandeling van tabaksverslaving en stoppen met roken ondersteuning'. *Ned tijschr geneekd, 161*:D1394. Retrieved from https://dspace.library.uu.nl/handle/1874/355597

Christenhusz, L.C.A. (2006). Smoking Cessation in COPD Patients: (Cost-)Effectiveness of the SmokeStopTherapy and Validation of Abstinence. Retrieved from https://ris.utwente.nl/ws/portalfiles/portal/6119687/thesis_Christenhusz.pdf

Civljak, M., Stead, L.F., Hartmann-Boyce, J., Sheikh, A., & Car, J. (2013). Internet-based interventions for smoking cessation. https://doi.org/10.1002/14651858.CD007078.pub4

CoVita. (2010). piCO+ Smokerlyzer operating manual. Retrieved from http://www.covita.net/pdfs/piCO+%20Manual.pdf.

Erbe, D., Eichert, H. C., Riper, H., & Ebert, D. D. (2017). Blending Face-to-Face and Internet -Based Interventions for the Treatment of Mental Disorders in Adults: Systematic Review. *Journal of medical Internet research*, *19*(9): e306. doi: 10.2196/jmir.6588

Feenstra, T.L., Hamburg-van Reenen, H.H., Hoogenveen, R.T., & Rutten-van Mölken, M.P.M.H. (2005). Cost-Effectiveness of Face-to-Face Smoking Cessation Interventions: A Dynamic Modeling Study. *Value in heath, 8*(3), 178-190. https://doi.org/10.1111/j.1524-4733.2005.04008.x

Fiore, M.C., Jaén, C.R., Baker, T.B., Bailey, W.C., Benowitz, N.L., Curry, S.J., … & Henderson, P.N. (2008). Treating Tabacco Use and Dependence: 2008 Update. *Rockeville, MD: US Department of Health and Human Services.* Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK63943/

Fitzpatrick, M., Nedeljkovic, M., Abbott, J. A., Kyrios, M., & Moulding, R. (2018). "Blended" therapy: The development and pilot evaluation of an internet-facilitated cognitive behavioral intervention to supplement face-to-face therapy for hoarding disorder. *Internet interventions, 12*, 16-25. https://doi.org/10.1016/j.invent.2018.02.006

Fryling, M.J., Wallace, M.D., Yassine, J.N. (2012). Impact of treatment integrity on intervention effectiveness. *J Appl Behav Anal, 45*(2), 449-453. doi 10.1901/jaba.2012.45-449

Gerhards. S.A., Abma, T.A., Arntz, A., de Graaf, L.E., Evers, S.M., Huibers, M.J.H., Widdershoven, G.A. (2011). Improving adherence and effectiveness of computerised cognitive behavioural therapy without support for depression: a qualitative study on patient experiences. *J Affect Disord., 129*, 117-125. doi 10.1016/j.jad.2010.09.012.

Hagens, P., Pieterse, M., Van der Valk, P., & Van der Palen, J. (2017). Effectiveness of intensive smoking reduction counselling plus combination nicotine replacement therapy in promoting long-term abstinence in patients with chronic obstructive pulmonary disease not ready to quit smoking: Protocol of the REDUQ trial. *Comtemp Clin Trials Commun.. 8* (2017), 248-257. http://dx.doi.org/10.1016/j.conctc.2017.08.014

Hahn, S. (2012). Understanding noninferiority trials. *Korean J Pediatr*, *55*(11), 403-407. doi: 10.3345/kjp.2012.55.11.403

Jorenby, D.E. (2001). Smoking Cessation Strategies for the 21st Century. *Circulation.* https://doi.org/10.1161/hc3601.097690

Karadogan, D., Ónal, Ö., Sahin, D.S., Kanbay, Y., Alp, S., Sahin, Ü. (2018). Treatment adherence and short-term outcomes of smoking cessation outpatient clinic patients. *Tob Induc Dis, 16.* doi 10.18332/tid/94212

Kelders, S.M., Kok, R.N., Ossebaard, H.C., van Gemert-Pijnen, J.E. (2012). Persuasive SystemDesign Does Matter: A Systematic Review of Adherence to Web-Based Interventions. *J Med Internet Res*, *14(*6):e152. doi 10.2196/jmir.2104

Kloek, C., Bossen, D., De Bakker, D. H., Veenhof, C., & Dekker, J. (2017). Blended interventions to change behavior in patients with chronic somatic disorders: systematic review. *Journal of medical Internet research*, *19*(12). doi: 10.2196/jmir.8108

Kooistra, L.C., Wiersma, J.E., Ruwaard, J., Neijenhuijs, K., Lokkerbol, J., van Oppen, P., & Riper, H. (2019). Cost and Effectiveness of Blended Versus Standard Cognitive Behavioral Therapy for Outpatients With Depression in Routine Specialized Mental Health Care: Pilot Randomized Controlled Trial. *Journal of medical Internet research*, *21*(10):e14261. doi: 10.2196/14261

Kuijper, K. (2019). 'Stoppen met roken' volledig vergoed door zorgverzekering (2020). Retrieved on June 12, 2020 from https://www.zorgwijzer.nl/zorgverzekering 2020/stoppen-met-roken-volledig-vergoed-door-zorgverzekering

Leu, E.R., Rutten, F.F.H., Brouwer, W., Matter, P., & Rütschi, C. (2009). The Swiss and Dutch Health Insurance Systems: Universal Coverage and Regulated Competitive Insurance Markets. Retrieved from https://www.issuelab.org/resources/11352/11352.pdf

Macaya, F., Ryan, N., Salinas, P., Pocock, S.J. (2017). Challenges in the Design and Interpretation of Noninferiority Trials. *Journal of the American College of Cardiology, 70*(7), 894-903. https://doi.org/10.1016/j.jacc.2017.06.039

Mansson, K.N.T., Ruiz, E.S., Gervind, E., Dahlin, M., Andersson, G. (2013). Development and Initial Evaluation of an Internet-Based Support System for Face-to-Face Cognitive

Behavior Therapy: A Proof of Concept Study. *J Med Internet Res, 15*(12):e280. doi: 10.2196/jmir.3031

Marsh, J.E., & Rajaram, S. (2019). The Digital Expansion of the Mind: Implications of Internet Usage for Memory and Cognition. *Journal of Applied Research in Memory and Cognition, 8*(1), 1-14. https://doi.org/10.1016/j.jarmac.2018.11.001

Michie, S., Hyder, N., Walia, A., & West, R. (2011). Development of a taxonomy of behaviour change techniques used in individual behavioural support for smoking cessation. *Addict Behav*, *36*(4), 315–319. https://doi.org/10.1016/j.addbeh.2010.11.016

Mol, M., van Genugten, C., Dozeman, E., van Schaik, D.J.F., Draisma, S., Riper, H., Smit, J.H. (2019). Why Uptake of Blended Internet-Based Interventions for Depression Is Challenging: A Qualitative Study on Therapists' Perspectives. *Journal of Clinical Medicine*, *9*(1), 91. https://doi.org/10.3390/jcm9010091

Mocher, F.J., Prinz, R.J. (1991). Treatment fidelity in outcome studies. *Clinical Psychology Review, 11*(3), 247-266. https://doi.org/10.1016/0272-7358(91)90103-2

Mossberger, K., Tolbert, C.J., & Stansbury, M. (2003). Virtual Inequality: Beyond the Digital Divide. Georgetown University Press, Washington, DC.

Patterson F, Jepson C, Kaufmann V, Rukstalis M, Audrain-McGovern J, Kucharski S, et al. (2003). Predictors of attendance in a randomized clinical trial of nicotine replacement therapy with behavioral counseling. *Drug Alcohol Depend*. *72*(2), 123-31. doi 10.1016/s03768716(03)00194-7

Ranjani, N.B., Weth, D., Mastellos, N., Filippidis, F.T. (2019). Adherence of popular smoking cessation mobile applications to evidence-based guidelines. *BMC Public Health, 19*. https://doi.org/10.1186/s12889-019-7084-7

Sabate, E. & Staff, W. (2003). Adherence to Long-Term Therapies: Evidence for Action. Geneva: World Health Organization. Retrieved from https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf

Sharma, P., Sane, N., Anand, S.D., Marimutthu, P., & Benegal, V. (2019). Assessment of cotinine in urine and saliva of smokers, passive smokers, and nonsmokers: Method validation using liquid chromatography and mass spectrometry. *Indian J Psychiatry, 61*(3), 270-276. doi: 10.4103/psychiatry.IndianJPsychiatry_61_18

Shiffman, S. (2005). Dynamic Influences on Smoking Relapse Process. *Journal of Personality, 73*(6). https://doi.org/10.1111/j.0022-3506.2005.00364.x

Siemer, L., Ben Allouch, S., Pieterse, M., Brusse-Keizer, M., Sanderman, R., Postel, M.G. (2020). Patients' User Experience of a Blended Face-to-Face and Web-Based Smoking Cessation Treatment: Qualitative Study. *Journal of Medical Internet Research, 4*(6):e14550. doi 10.2196/14550

Siemer, L., Brusse-Keizer, M., Postel, M.G., Ben Allouch, S., Patrinopoulos, A., Sanderman, R., & Pieterse, M.E. (2018). Blended Smoking Cessation Treatment: Exploring Measurement, Levels, and Predictors of Adherence. *Journal of Medical Internet Research, 20*(8). doi 10.2196/jmir.9969

Siemer, L., Pieterse, M.E, Ben Allouch, S., Postel, M.G., Sanderman, R., & Brusse-Keizer, M.G.J. (2020). Comparing Effectiveness and Initial Evaluation of a Blended Smoking Cessation Treatment to Face-to-Face Treatment: Intermediate Outcomes of a Randomized Controlled Non-Inferiority Trial. *Addiction.* Unpublished manuscript.

Siemer, L., Pieterse, M., Brusse-Keizer, M., Postel, M.G., Ben Allouch, S., & Sanderman, R. (2016). Study protocol for a non-inferiority trial of a blended smoking cessation treatment versus face-to-face treatment (LiveSmokefree-Study). *BMC Public Health, 16*(1). doi 10.1186/s12889-016-3851-x

Szumilas, M. (2010). Explaining Odds Ratios. *Journal of the Canadian academy of child and adolescent psychiatry, 19*(3*),* 227-229. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938757/

Trimbos instituut. (2020). Cijfers roken. *Netherlands institute of Mental Health and Addiction* Retrieved from https://www.trimbos.nl/kennis/cijfers/cijfers-roken

Trimbos instituut. (2016). Herziening behandeling van tabaksverslaving en stoppen met roken ondersteuning, herziening 2016. *Netherlands Institute of Mental Health and Addiction.* Retrieved from https://www.trimbos.nl/docs/7435d8f9-c8f4-4302-aec6 f4fddade81f2.pdf

U.K. Department of Health. (2014). A compendium of factsheets: wellbeing across the lifecourse: the relationship between wellbeing and health [Fact sheet]. Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachm nt_data/file/295474/The_relationship_between_wellbeing_and_health.pdf

van Aerde, M., Croes, E., Willemsen, M. (2020). *Roken is een verslaving.* Retrieved on March 19, 2020 from https://www.trimbos.nl/docs/708f4ef3-2552-405a-ab7a -e97634c7ba54.pdf

van der Vaart, R., Witting, M., Riper, H., Kooistra, L., Bohlmeijer, E., van Gemert-Pijnen, LJ. (2014). Blending online therapy into regular face-to-face therapy for depression: content, ratio  and preconditions according to patients and therapists using a Delphi study. *BMC    Psychiatry, 14*, 355. https://doi.org/10.1186/s12888-014-0355-z

Waller, G. (2009). Empirisch onderbouwde therapie en therapist drift. *Behavior Research and Therapy,         47*(2),         119-127.         Retrieved         from https://www.tijdschriftgedragstherapie.nl/inhoud/tijdschrift_artikel/TG-2014-3 -5/Empirisch-onderbouwde-therapie-en-therapist-drift

West. R., Walia, A., Hyder, N., Shahab, L., Michie, S. (2010). Behavior change techniques used by the English Stop Smoking Services and their associations with short-term quit outcomes. *Nicotine    &    Tobacca    Research*,    *12*(7),    742–747. https://doi.org/10.1093/ntr/ntq074

WHO    (2014).    Tabaco    Fact    Sheet    Nº339.    Retrieved    from https://www.who.int/healthsystems/topics/health-law/chapter13.pdf

WHO (2019). *Tabaco.* Retrieved from https://www.who.int/news

room/fact-sheets/detail/tobacco

Wilson, H. & Sherman, S. (2016).  In adults, quitting smoking abruptly improved abstinence more than quitting gradually. *Ann Intern Med*, *165*(2):JC3. doi: 10.7326/ACPJC-2016 165-2-003

# Appendix 1

Distribution of the behaviour change techniques in face-to-face (F2F) and blended treatment (BSCT)

As quoted from Siemer et al. (2016).

| Session/week/<br>main goal of session | Main behavioural change techniques according to CBO (2009) | F2F | BSCT |
|---|---|---|---|
| Session 1, week 1<br>Goal setting | Provide information on consequences of smoking and smoking cessation (BM1)<br>Provide rewards contingent on successfully stopping smoking (BM4)<br>Identify reasons for wanting and not wanting to stop smoking (BM9)<br>Facilitate goal setting (BS4)<br>Prompt self-recording (BS6)<br>Advise on stop-smoking medication (A1)<br>Advise on/facilitate use of social support (A2)<br>Build general rapport (RC1)<br>Explain expectations regarding treatment programme (RC4) | Face-to-face | Face-to-face |
| Session 2, week 3<br>Measures for self-control | Provide feedback on current behaviour (BM3)<br>Provide rewards contingent on effort or progress (BM7)<br>Facilitate barrier identification and problem solving (BS1)<br>Facilitate relapse prevention and coping (BS2)<br>Prompt review of goals (BS5)<br>Prompt self-recording (BS6)<br>Advise on changing routine (BS7)<br>Tailor interactions appropriately (RD1) | Face-to-face | Web-based |
| Session 3, week 5<br>Dealing with withdrawal | Provide feedback on current behaviour (BM3)<br>Provide normative information about others' behaviour and experiences (BM5)<br>Facilitate relapse prevention and coping (BS2) | Face-to-face | Face-to-face |

| | Prompt self-recording (BS6)<br>Provide information on withdrawal symptoms (RC6)<br>Provide reassurance (RC10) | | |
|---|---|---|---|
| Session 4, week 7<br>Breaking habits | Provide feedback on current behaviour (BM3)<br>Provide normative information about others' behaviour and experiences (BM5)<br>Facilitate barrier identification and problem solving (BS1)<br>Facilitate relapse prevention and coping (BS2)<br>Advise on changing routine (BS7)<br>Advise on conserving mental resources (BS10)<br>Advise on avoiding social cues for smoking (BS11)<br>Advise on/facilitate use of social support (A2)<br>Provide reassurance (RC10) | Face-to-face | Web-based |
| Session 5, week 9<br>Dealing with triggers | Provide rewards contingent on effort or progress (BM7)<br>Facilitate relapse prevention and coping (BS2) | Face-to-face | Face-to-face |
| Session 6, week 11<br>Food for thought | Provide feedback on current behaviour (BM3)<br>Offer/direct towards appropriate written materials (RC5)<br>Elicit client views (RC8) | Face-to-face | Web-based |
| Session 7, week 14<br>Think differently | Provide feedback on current behaviour (BM3)<br>Measure CO (BM11)<br>Facilitate barrier identification and problem solving (BS1)<br>Facilitate relapse prevention and coping (BS2)<br>Prompt self-recording (BS6)<br>Build general rapport (RC1)<br>Elicit and answer questions (RC2) | Face-to-face | Face-to-face |
| Session 8, week 18<br>Do differently | Provide feedback on current behaviour (BM3)<br>Facilitate barrier identification and problem solving (BS1)<br>Facilitate relapse prevention and coping (BS2) | Face-to-face | Online |

| | | | |
|---|---|---|---|
| | Prompt self-recording (BS6)<br>Tailor interactions appropriately (RD1)<br>Build general rapport (RC1) | | |
| Session 9, week 22<br>Action plan | Provide feedback on current behaviour (BM3)<br>Measure CO (BM11)<br>Facilitate action planning/develop treatment plan (BS3)<br>Build general rapport (RC1)<br>Elicit client views (RC8) | Face-to-face | Face-to-face |
| Session 10, week 26<br>Closure | Provide feedback on current behaviour (BM3)<br>Provide rewards contingent on successfully stopping smoking (BM4)<br>Strengthen ex-smoker identity (BM8)<br>Facilitate barrier identification and problem solving (BS1)<br>Facilitate relapse prevention and coping (BS2)<br>Facilitate goal setting (BS4)<br>Set graded tasks (BS9)<br>Advise on/facilitate use of social support (A2)<br>Build general rapport (RC1)<br>Offer/direct towards appropriate written materials (RC5)<br>Elicit client views (RC8) | Face-to-face | Web-based |

Codes: BM = Specific focus on behaviour (B) and addressing motivation (M); BS = Specific focus on behaviour (B) and maximising self-regulatory capacity/skills (S); A = Promote adjuvant activities (A); RC = General aspects of the interaction (R) focusing on general communication (C); RD = General aspects of the interaction (R) focusing on delivery of the intervention (D)