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**Effect of a Smartphone Application on Medication Adherence and Blood Pressure Control:  
The MedISAFE-BP Randomized Clinical Trial**

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29 Initial protocol

30

31 ***Introduction***

32 Hypertension is a major factor in health issues such as stroke, heart disease, and kidney disease.  
33 Worldwide there are 9.4 million deaths each year that can be attributed to hypertension and its effects  
34 through cardiovascular disease (1). It has been estimated that annual medical expenditures of \$46 billion  
35 can be attributed to hypertension in the United States (2). Medications exist for the treatment of  
36 hypertension and can prevent the harmful effects of elevated blood pressure and its associated morbidities  
37 and mortalities, but medication adherence is a known barrier to effective treatment (3-5).

38 The rapid adoption of smartphone technologies (6) makes this an attractive avenue to influence  
39 health practices, primarily medication adherence and subsequent blood pressure control. Smartphone  
40 applications can deliver reminders about medication administration to encourage the proper timing and  
41 adherence to prescriptions, provide education about healthy behaviors in life, be a means for loved-ones  
42 to check in, create a network of patients to form a support system through social media, and monitor  
43 biometric measurements.

44 Previous studies have examined the impact on hypertension of a smartphone application paired  
45 with an on-call medical professional (1) or the effect of tele-monitoring (17, 19, 20) and found  
46 improvements in blood pressure. Other smartphone-based interventions have been performed in people  
47 with elevated cardiovascular risk, but have focused on text messages that are semi-personalized to the  
48 patient (18). The impact of a stand-alone smartphone application on blood pressure has not been tested in  
49 a rigorous manner, especially with regards to clinically meaningful outcomes of hypertension control.  
50 Medisafe was developed to address non-adherence, and provide alerts to patients when it is time to take  
51 their medications. Other features include the ability to allow a “Medfriend” to check in if a medication is  
52 not taken, weekly reports of medication adherence, and monitoring of biometric measurements (either  
53 directly into the application, or through synchronization with the smartphone’s health applications).

54

55 **Objectives and Overall Study Design**

56 The Medication adherence Improvement Support App For Engagement – Blood Pressure  
57 (MEDISAFE–BP) trial is a prospective, intent-to-treat randomized control trial that aims to evaluate the  
58 impact of the Medisafe smart application on blood pressure control and self-reported medication  
59 adherence for patients with uncontrolled blood pressure.

60

61 **Patient Eligibility**

<i>Inclusion</i>	<i>Exclusion</i>
<ul style="list-style-type: none"><li>• <math>\geq 18</math> and <math>\leq 75</math> years of age</li><li>• Self-reported systolic blood pressure <math>\geq 140</math> mmHg</li><li>• Self-reported active prescription of 1-3 of the following anti-HTN medications (thiazide, CCB, <math>\beta</math>-blocker, ACE-I, ARB)</li><li>• Systolic blood pressure <math>\geq 140</math> mmHg (+/- diastolic blood pressure <math>\geq 90</math> mmHg), but blood pressure <math>\leq 180/120</math> mmHg confirmed by home BP-cuff (see below)</li></ul>	<ul style="list-style-type: none"><li>• Current use of a smartphone medication adherence application</li><li>• No ownership of a smartphone with iOS or compatible Android operating system</li><li>• Currently taking <math>&gt; 3</math> anti-HTN medications (thiazide, CCB, <math>\beta</math>-blocker, ACE-I, ARB) by self-report</li><li>• Currently undergoing dialysis</li><li>• Currently receiving chemotherapy or radiation</li><li>• Does not understand English</li></ul>

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63 ***Subject Recruitment and Randomization***

64 Recruitment will be conducted by Evidation Health, which uses an online strategy to virtually  
65 announce, recruit, verify eligibility and enroll participants in clinical studies. Subjects will be recruited  
66 through various digital platforms such as online patient communities, social media, pertinent mobile  
67 applications, and targeted advertisements. As shown in Figure 1, potential study subjects will be  
68 evaluated for inclusion and exclusion criteria, will give informed consent, complete the baseline  
69 assessment, and then be sent a Bluetooth-enabled home blood pressure cuff to verify that they have  
70 uncontrolled blood pressure (systolic blood pressure  $\geq 140$  mmHg but overall blood pressure  $\leq 180/120$   
71 mmHg). Patients will be provided with a study overview and blood pressure measurement guide that will  
72 outline how to set up the monitor and take an accurate measurement, as well as the standard insert for  
73 how to use the home monitor and its associated smartphone application. Blood pressure readings will be  
74 electronically transmitted to Evidation Health via an Application Program Interface (API) with the blood  
75 pressure monitor manufacturer. If patients are unable to activate the smartphone application associated  
76 with the blood pressure monitor, they may submit their blood pressure readings by taking a time-stamped  
77 photo of the blood pressure monitor display. Blood pressure will be calculated as the average of two  
78 measurements that are taken five minutes apart, which is in accordance with previous literature (14).  
79 Once their blood pressure readings have been confirmed as being elevated, patients will undergo  
80 randomization in a 1:1 ratio to intervention or control using simple randomization through a random  
81 number generated at the time of study enrollment.

82

83 ***Informed Consent***

84 Informed consent will be attained from subjects prior to enrollment using an eConsent process.  
85 Patients will be told that a study is being conducted for evaluation of blood pressure, and focused on  
86 strategies to optimize treatment using technology. They will also be informed of how their personal

87 information will be secured and that all analysis will be conducted on de-identified data. Because  
88 Medisafe is a free application and notification may lead to use of this technology in the control arm,  
89 patients will not be told about Medisafe before randomization. After randomization patients in the  
90 intervention arm will be provided with information and instructions to download Medisafe. During the  
91 informed consent process, there will be a contact form as well as a phone number and email available to  
92 patients for any questions or to withdraw from the study.

93

#### 94 ***Study Procedures***

95 Prior to randomization, patients will be asked to complete a baseline assessment. This will  
96 consist of baseline demographics including cardiovascular comorbidities, use of cigarettes, and education  
97 level (15). The Morisky 8-item adherence scale will also be collected, which has been validated to  
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99 knowledge will also be assessed in accordance with Oliveira et. al (16). Subjects will also be asked to  
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103 Patients assigned to the intervention arm will be emailed with instructions to download the  
104 Medisafe application. Through an integration with Medisafe, Evidation Health will confirm that the  
105 application has been downloaded and launched at least once within two days from randomization.  
106 Patients who do not download and launch the application at least once within two days will be contacted  
107 by email two more times and provided the instructions for download until they launch the application. If  
108 they still do not launch the application, they will be contacted twice via telephone, then one final time by  
109 email. If after three reminder e-mails and two phone calls the participant still does not launch the

110 application, they will not be contacted further about downloading the application, but they will remain in  
111 the intent-to-treat analysis group.

112 Patients assigned to the control arm will not receive any intervention.

113 At two time points, four and eight weeks after randomization, all subjects assigned to intervention  
114 and control will be e-mailed and asked to measure their blood pressure using the Bluetooth-enabled blood  
115 pressure cuff and its associated smartphone application (all blood pressures will be done via two  
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118 sent until a blood pressure measurement is received. If there is still no blood pressure measurement  
119 received, two phone calls will be made to the study participant, followed by one final email reminder. If  
120 they are unable to be reached by three reminder e-mails and two phone calls, they will not be contacted  
121 again for that blood pressure measurement, but will be contacted to obtain the next assessment (either 8-  
122 week blood pressure measurement or study exit assessment) and will remain in the intent-to-treat analysis  
123 group.

124 At 12 weeks, all subjects will be asked to complete an exit questionnaire consisting of Morisky 8-  
125 item medication adherence scale (8), hypertension knowledge questionnaire (16), and a CHAI. They will  
126 also be asked to take their final blood pressure measurement. The same protocol described above of three  
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128 sequence of 2 reminder emails, 2 phone calls, 2 reminder emails), should there be a delay in answering  
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130 questionnaire or take their final blood pressure measurement will be lost to follow-up. After completing  
131 the study, subjects will be given the option to keep the blood pressure cuff or donate it to an organization  
132 that recycles digital health and wellness products for underserved populations.

133           Subjects may choose to take blood pressure measurements using the Bluetooth-enabled blood  
134 pressure cuff more often than the four readings required in the study. That data will also be transmitted to  
135 Evidation Health via the API and stored in the study database.

136           Throughout the study, subject data including blood pressure measurements and survey data will  
137 be reviewed to ensure data quality and consistency. Patients may be contacted by phone or email to  
138 address suspicious or unusual data submissions.

139           All study subjects will be provided compensation for their time to participate in the study, staged  
140 in four intervals throughout the study (i.e., after randomization, after submitting blood pressure  
141 measurement at 4 and 8 weeks after enrollment respectively, and after completion of final blood pressure  
142 measurement and exit questionnaire). Maximum total compensation per study subject will not exceed  
143 \$150.

144

#### 145 ***Data Security and Confidentiality***

146           All identifiable information about patients, their medical conditions, and other study data will be  
147 secured by Evidation Health in accordance with all local and state laws, regulations and Human Subjects  
148 Committee policies regarding collection and distribution of patient information. Evidation Health will use  
149 a HIPAA compliant survey system to collect the participant information and consent. Participant  
150 information received from smartphone applications will be transmitted using Transport Layer Security  
151 (TLS).

152           Data will only be stored electronically. All PHI and PII will be stored only on a single secured  
153 server in the Amazon EC2 cloud designed exclusively for this purpose. The server will be protected by  
154 two-factor authentication (requiring a password and a code generated on a separate device that changes  
155 every 60 seconds). All communication with the server will be encrypted using TLS. Only Evidation

156 Health's VP of Engineering and Head of Operations will have access to server. Data will be encrypted at  
157 rest.

158 De-identified data will be stored on a separate password-secured server with data at rest  
159 encryption. Only Evidation Health's Head of Operations and Data Science and Data Engineering teams  
160 have access to this server. Only de-identified data will be transferred to the Center for Healthcare  
161 Delivery Science (C4HDS) at Brigham Women's Hospital. Questionnaire data and other de-identified  
162 data will only be linked to PHI and PII through a unique study-generated identifier. This identifier will be  
163 generated via a secure cryptographic hash that cannot be reverse-engineered.

164

#### 165 ***Outcomes***

166 The study's co-primary outcomes will be a change in systolic blood pressure from randomization  
167 to three months later and self-reported medication adherence (see Table 1). The secondary outcome will  
168 be change in number of subjects who have well controlled blood pressure (<140/90 mmHg).

169

#### 170 ***Analytic Plan***

171 The Center for Healthcare Delivery Science (C4HDS) at Brigham Women's Hospital will  
172 conduct all analysis on de-identified data. We will report baseline patient characteristics and evaluate  
173 differences in the two groups to identify any potentially unmatched covariates despite randomization. We  
174 will plot changes in blood pressure over time.

175 Analyses will be performed by an intent-to-treat basis, where subjects will be analyzed in the  
176 groups they are assigned to during randomization. We will use linear regression to assess the impact of  
177 Medisafe on the study's 2 primary outcomes (change in systolic blood pressure and self-reported  
178 adherence) between the two study groups, 3 months after randomization. Our primary models will adjust



179 for unbalanced covariates between the two groups. Only the initial and 12-week blood pressure readings  
180 will be included in the primary analysis.

181 In secondary analyses, we will determine the number of patients that had their hypertension  
182 controlled (i.e., <140/90mmHg) during the study period in both arms, and calculate an odds ratio using  
183 multivariate logistic regression in order to control for potentially unmatched baseline covariates. We will  
184 also repeat our analyses with longitudinal modeling methods that incorporate blood pressure readings at  
185 4, 8, and 12 weeks after randomization. If there are additional blood pressure readings from patients who  
186 took their blood pressure more often than required, we will include this data in exploratory longitudinal  
187 modeling analyses.

188 In supplemental analyses, we will evaluate whether the impact of Medisafe differed for subjects  
189 who interacted with Medisafe frequently (defined as being in the upper median of use for the Medisafe  
190 application based on frequency of user sessions during the study period) as compared to subjects who  
191 interacted with Medisafe less frequently. We will perform this analysis by including categorical variables  
192 for high and low use in our outcome model, whereby control subjects are indicating by null values for  
193 both of these indicators. We will also evaluate effect modification by hypertension knowledge (16)  
194 recorded at baseline.

195

### 196 *Sample Size*

197 With a change in systolic blood pressure of 5mmHg, which has previously been shown to be  
198 clinically significant (12,13), a standard deviation of 17mmHg, a power of 80%, and an alpha of 0.05  
199 there would need to be 312 patients enrolled. With allowance for 20% loss to follow-up, the study will  
200 seek to enroll 390 patients total to have an 80% power with an alpha of 5%. With a standard deviation of  
201 1.6 (8) and a sample size of 390 patients, we will be able to detect a 0.5 Morisky score difference between  
202 the groups with a power of 87%.

203

204 ***Risks Associated with the Intervention***

205           Since the intervention under investigation is not aimed at altering a patient’s treatment, but rather  
206 to promote adherence to treatments that they have already been prescribed, the risk will be minimal.  
207 There is a possible risk of patients receiving escalating anti-hypertensive medications from their treatment  
208 team due to non-adherence, and with the better adherence through Medisafe reminders there could be  
209 medication induced hypotension. During the informed consent process and on the blood pressure  
210 measurement guidance sheet there will be recommendations to reach out to their treatment team if they  
211 ever have a blood pressure > 180/120 mmHg or < 90/50 mmHg. The informed consent will also clearly  
212 state that no component of the study, including the home blood pressure cuff use and study personnel, is a  
213 replacement for care from a health care professional.

214           The likelihood that a study participant has a blood pressure reading > 180/120 mmHg or < 90/50  
215 mmHg during the study is very low, since this is a low-risk patient population. Inclusion criteria is limited  
216 to patients with stage I or II hypertension, and patients with an initial blood pressure reading > 180/120  
217 mmHg will be excluded. Patients taking more than three anti-hypertensive medications will also be  
218 excluded. Additionally, patients will be notified during the informed consent process that their blood  
219 pressure readings will not be monitored by the research team, and that they should reach out to their  
220 treatment team if their blood pressure is ever very high or very low.

221 Final protocol

222

223 ***Introduction***

224 Hypertension is a major factor in health issues such as stroke, heart disease, and kidney disease.  
225 Worldwide there are 9.4 million deaths each year that can be attributed to hypertension and its effects  
226 through cardiovascular disease (1). It has been estimated that annual medical expenditures of \$46 billion  
227 can be attributed to hypertension in the United States (2). Medications exist for the treatment of  
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236 Previous studies have examined the impact on hypertension of a smartphone application paired  
237 with an on-call medical professional (1) or the effect of tele-monitoring (17, 19, 20) and found  
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<i>Inclusion</i>	<i>Exclusion</i>
<ul style="list-style-type: none"><li>● <math>\geq 18</math> years of age</li><li>● Self-reported blood pressure <math>\geq 140/90</math> mmHg</li><li>● Self-reported active prescription of 1-3 of the following anti-HTN medications (thiazide, CCB, <math>\beta</math>-blocker, ACE-I, ARB)</li><li>● Blood pressure <math>\geq 140/90</math> mmHg, but <math>\leq 180/120</math> mmHg confirmed by home BP-cuff (see below)</li></ul>	<ul style="list-style-type: none"><li>● Current use of a smartphone medication adherence application</li><li>● Current use of an automated home blood pressure cuff</li><li>● No ownership of a smartphone with iOS or compatible Android operating system</li><li>● Currently taking <math>&gt; 3</math> anti-HTN medications (thiazide, CCB, <math>\beta</math>-blocker, ACE-I, ARB) by self-report</li><li>● Currently undergoing dialysis</li><li>● Currently receiving chemotherapy or radiation</li></ul>

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329   address suspicious or unusual data submissions.

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332   measurement at 4 and 8 weeks after enrollment respectively, and after completion of final blood pressure  
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336   ***Data Security and Confidentiality***

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343           Data will only be stored electronically. All PHI and PII will be stored only on a single secured  
344   server in the Amazon EC2 cloud designed exclusively for this purpose. The server will be protected by  
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347 Health's VP of Engineering and Head of Operations will have access to server. Data will be encrypted at  
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349 De-identified data will be stored on a separate password-secured server with data at rest  
350 encryption. Only Evidation Health's Head of Operations and Data Science and Data Engineering teams  
351 have access to this server. Only de-identified data will be transferred to the Center for Healthcare  
352 Delivery Science (C4HDS) at Brigham Women's Hospital. Questionnaire data and other de-identified  
353 data will only be linked to PHI and PII through a unique study-generated identifier. This identifier will be  
354 generated via a secure cryptographic hash that cannot be reverse-engineered.

355

#### 356 ***Outcomes***

357 The study's co-primary outcomes will be a change in blood pressure from randomization to three  
358 months later and self-reported medication adherence (see Table 1). The secondary outcome will be  
359 change in number of subjects who have well controlled blood pressure (<140/90 mmHg).

360

#### 361 ***Analytic Plan***

362 The Center for Healthcare Delivery Science (C4HDS) at Brigham Women's Hospital will  
363 conduct all analysis on de-identified data. Analyses will be performed by an intent-to-treat basis, where  
364 subjects will be analyzed in the groups they are assigned to during randomization.

365 We will begin by comparing the baseline patient characteristics in each of the arms using t-tests,  
366 chi-square tests or their non-parametric analogues, as appropriate. We will evaluate for rates of missing  
367 data between the two study arms to ensure that it is non-differential.

368 We will use linear regression to assess the impact of Medisafe on the study's 2 primary outcomes  
369 (change in blood pressure and self-reported adherence) between the two study groups. Our null

370 hypothesis will be that there is no difference in the change in blood pressure between the two groups after  
371 12 weeks.

372 Our primary models will adjust for unbalanced covariates between the two groups (i.e. age,  
373 gender, ethnicity, BMI, comorbidities, number of antihypertensive medications, total number of  
374 medications, education, exercise level, cell phone use) should any exist using a p-value threshold of 0.05  
375 and will impute missing outcome data where 12 week outcome data is unavailable. Imputation will be  
376 performed using the PROC MI command in SAS and will include the covariates defined above as well as  
377 intermediate outcomes (i.e. blood pressure at weeks 4 and 8). Multiple imputation with 5 imputations  
378 will be used and the imputed values will be inspected to ensure in-range values. After imputation,  
379 analyses will be conducted on the imputed data set and the results will be combined using the standard  
380 rules from Rubin et al. In sensitivity analyses, we will analyze only those subjects for whom we have  
381 complete outcome data (i.e. a complete case analysis).

382 In secondary analyses, we will determine the number of patients that had their hypertension  
383 controlled (i.e., <140/90mmHg) during the study period in both arms, and calculate an odds ratio using  
384 multivariate logistic regression with covariates indicated above. In supplemental analyses, we will repeat  
385 our analyses with longitudinal modeling methods that incorporate blood pressure readings at 4, 8, and 12  
386 weeks after randomization. This will be done using generalized estimating equations to account for  
387 correlations between repeated blood pressure readings for any individual subjects. If there are additional  
388 blood pressure readings from patients who took their blood pressure more often than required, the  
389 longitudinal models will be re-run to include these additional values.

390 In subgroup analyses, we will evaluate whether the impact of Medisafe differed for subjects who  
391 interacted with Medisafe frequently (defined as being in the upper median of use for the Medisafe  
392 application based on number of days logged in during the study period) as compared to subjects who  
393 interacted with Medisafe less frequently. We will perform this analysis by including categorical variables  
394 for high and low use in our outcome model, whereby control subjects are indicating by null values for

395 both indicators. We will also evaluate effect modification by hypertension knowledge (16) recorded at  
396 baseline.

397

398 ***Sample Size***

399 With a change in blood pressure of 5mmHg, which has previously been shown to be clinically  
400 significant (12,13), a standard deviation of 16.7mmHg, a power of 80%, and an alpha of 0.05 there would  
401 need to be 312 patients enrolled. With allowance for 20% loss to follow-up, the study will seek to enroll  
402 390 patients total to have an 80% power with an alpha of 5%. With a standard deviation of 1.6 (8) and a  
403 sample size of 390 patients, we will be able to detect a 0.5 Morisky score difference between the groups  
404 with a power of 87%.

405

406 ***Risks Associated with the Intervention***

407 Since the intervention under investigation is not aimed at altering a patient's treatment, but rather  
408 to promote adherence to treatments that they have already been prescribed, the risk will be minimal.  
409 There is a possible risk of patients receiving escalating anti-hypertensive medications from their treatment  
410 team due to non-adherence, and with the better adherence through Medisafe reminders there could be  
411 medication induced hypotension. During the informed consent process and on the blood pressure  
412 measurement guidance sheet there will be recommendations to reach out to their treatment team if they  
413 ever have a blood pressure > 180/120 mmHg or < 90/50 mmHg. The informed consent will also clearly  
414 state that no component of the study, including the home blood pressure cuff use and study personnel, is a  
415 replacement for care from a health care professional.

416 The likelihood that a study participant has a blood pressure reading > 180/120 mmHg or < 90/50  
417 mmHg during the study is very low, since this is a low-risk patient population. Inclusion criteria is limited

418 to patients with stage I or II hypertension, and patients with an initial blood pressure reading > 180/120  
419 mmHg will be excluded. Patients taking more than three anti-hypertensive medications will also be  
420 excluded. Additionally, patients will be notified during the informed consent process that their blood  
421 pressure readings will not be monitored by the research team, and that they should reach out to their  
422 treatment team if their blood pressure is ever very high or very low.

423

424 Summary of changes to protocol

425

Date of submission	Description of modification	Rationale for modification
	Changes in inclusion criteria as follows. Initial: <ul style="list-style-type: none"> <li>• <math>\geq 18</math> and <math>\leq 75</math> years of age</li> <li>• Self-reported systolic blood pressure <math>\geq 140</math> mmHg</li> <li>• Systolic blood pressure <math>\geq 140</math> mmHg (+/- diastolic blood pressure <math>\geq 90</math> mmHg), but blood pressure <math>\leq 180/120</math> mmHg confirmed by home BP-cuff</li> </ul> Final: <ul style="list-style-type: none"> <li>• <math>\geq 18</math> years of age</li> <li>• Self-reported blood pressure <math>\geq 140/90</math> mmHg</li> <li>• Blood pressure <math>\geq 140/90</math> mmHg, but <math>\leq 180/120</math> mmHg confirmed by home BP-cuff</li> </ul>	Removed restriction to individuals $\leq 75$ years of age and clarifying poorly-controlled BP as being defined based on both systolic and diastolic BP
	Addition to exclusion criteria of current use of an automated home blood pressure cuff	Required patients to not currently be using home blood pressure monitors to standardize outcome evaluation
	Change in primary outcome as follows. Initial: <ul style="list-style-type: none"> <li>• Change in systolic blood pressure from randomization to three months later</li> </ul> Final: <ul style="list-style-type: none"> <li>• Change in blood pressure from randomization to three months later</li> </ul>	To reflect the updated inclusion/exclusion criteria

426

427 For a description of changes to the analytic plan, see sections below.

428

429 Initial analytic plan

430 *Analytic Plan*

431 The Center for Healthcare Delivery Science (C4HDS) at Brigham Women’s Hospital will  
432 conduct all analysis on de-identified data. We will report baseline patient characteristics and evaluate  
433 differences in the two groups to identify any potentially unmatched covariates despite randomization. We  
434 will plot changes in blood pressure over time.

435 Analyses will be performed by an intent-to-treat basis, where subjects will be analyzed in the  
436 groups they are assigned to during randomization. We will use linear regression to assess the impact of  
437 Medisafe on the study’s 2 primary outcomes (change in systolic blood pressure and self-reported  
438 adherence) between the two study groups, 3 months after randomization. Our primary models will adjust  
439 for unbalanced covariates between the two groups. Only the initial and 12-week blood pressure readings  
440 will be included in the primary analysis.

441 In secondary analyses, we will determine the number of patients that had their hypertension  
442 controlled (i.e., <140/90mmHg) during the study period in both arms, and calculate an odds ratio using  
443 multivariate logistic regression in order to control for potentially unmatched baseline covariates. We will  
444 also repeat our analyses with longitudinal modeling methods that incorporate blood pressure readings at  
445 4, 8, and 12 weeks after randomization. If there are additional blood pressure readings from patients who  
446 took their blood pressure more often than required, we will include this data in exploratory longitudinal  
447 modeling analyses.

448 In supplemental analyses, we will evaluate whether the impact of Medisafe differed for subjects  
449 who interacted with Medisafe frequently (defined as being in the upper median of use for the Medisafe  
450 application based on frequency of user sessions during the study period) as compared to subjects who  
451 interacted with Medisafe less frequently. We will perform this analysis by including categorical variables  
452 for high and low use in our outcome model, whereby control subjects are indicating by null values for

453 both of these indicators. We will also evaluate effect modification by hypertension knowledge (16)  
454 recorded at baseline.

455

456 *Sample Size*

457 With a change in systolic blood pressure of 5mmHg, which has previously been shown to be  
458 clinically significant (12,13), a standard deviation of 17.6mmHg, a power of 80%, and an alpha of 0.05  
459 there would need to be 312 patients enrolled. With allowance for 20% loss to follow-up, the study will  
460 seek to enroll 390 patients total to have an 80% power with an alpha of 5%. With a standard deviation of  
461 1.6 (8) and a sample size of 390 patients, we will be able to detect a 0.5 Morisky score difference between  
462 the groups with a power of 87%.

463

464 Final analytic plan

465 *Analytic Plan*

466 The Center for Healthcare Delivery Science (C4HDS) at Brigham Women's Hospital will  
467 conduct all analysis on de-identified data. Analyses will be performed by an intent-to-treat basis, where  
468 subjects will be analyzed in the groups they are assigned to during randomization.

469 We will begin by comparing the baseline patient characteristics in each of the arms using t-tests,  
470 chi-square tests or their non-parametric analogues, as appropriate. We will evaluate for rates of missing  
471 data between the two study arms to ensure that it is non-differential.

472 We will use linear regression to assess the impact of Medisafe on the study's 2 primary outcomes  
473 (change in blood pressure and self-reported adherence) between the two study groups. Our null  
474 hypothesis will be that there is no difference in the change in blood pressure between the two groups after  
475 12 weeks.

476 Our primary models will adjust for unbalanced covariates between the two groups (i.e. age,  
477 gender, ethnicity, BMI, comorbidities, number of antihypertensive medications, total number of  
478 medications, education, exercise level, cell phone use) should any exist using a p-value threshold of 0.05  
479 and will impute missing outcome data where 12 week outcome data is unavailable. Imputation will be  
480 performed using the PROC MI command in SAS and will include the covariates defined above as well as  
481 intermediate outcomes (i.e. blood pressure at weeks 4 and 8). Multiple imputation with 5 imputations  
482 will be used and the imputed values will be inspected to ensure in-range values. After imputation,  
483 analyses will be conducted on the imputed data set and the results will be combined using the standard  
484 rules from Rubin et al. In sensitivity analyses, we will analyze only those subjects for whom we have  
485 complete outcome data (i.e. a complete case analysis).

486 In secondary analyses, we will determine the number of patients that had their hypertension  
487 controlled (i.e., <140/90mmHg) during the study period in both arms, and calculate an odds ratio using



488 multivariate logistic regression with covariates indicated above. In supplemental analyses, we will repeat  
489 our analyses with longitudinal modeling methods that incorporate blood pressure readings at 4, 8, and 12  
490 weeks after randomization. This will be done using generalized estimating equations to account for  
491 correlations between repeated blood pressure readings for any individual subjects. If there are additional  
492 blood pressure readings from patients who took their blood pressure more often than required, the  
493 longitudinal models will be re-run to include these additional values.

494 In subgroup analyses, we will evaluate whether the impact of Medisafe differed for subjects who  
495 interacted with Medisafe frequently (defined as being in the upper median of use for the Medisafe  
496 application based on number of days logged in during the study period) as compared to subjects who  
497 interacted with Medisafe less frequently. We will perform this analysis by including categorical variables  
498 for high and low use in our outcome model, whereby control subjects are indicating by null values for  
499 both indicators. We will also evaluate effect modification by hypertension knowledge (16) recorded at  
500 baseline.

501

#### 502 *Sample Size*

503 With a change in blood pressure of 5mmHg, which has previously been shown to be clinically  
504 significant (12,13), a standard deviation of 17.6mmHg, a power of 80%, and an alpha of 0.05 there would  
505 need to be 312 patients enrolled. With allowance for 20% loss to follow-up, the study will seek to enroll  
506 390 patients total to have an 80% power with an alpha of 5%. With a standard deviation of 1.6 (8) and a  
507 sample size of 390 patients, we will be able to detect a 0.5 Morisky score difference between the groups  
508 with a power of 87%.

509

510 Summary of changes to analytic plan

511 More concrete analysis methods for evaluating baseline patient characteristics as well as a list of  
512 potentially unmatched covariates are now provided which was not included in the original plan. Missing  
513 12-week outcome data is also addressed in the final plan, specifically performing multiple imputation via  
514 the PROC MI function in SAS.