

Smile

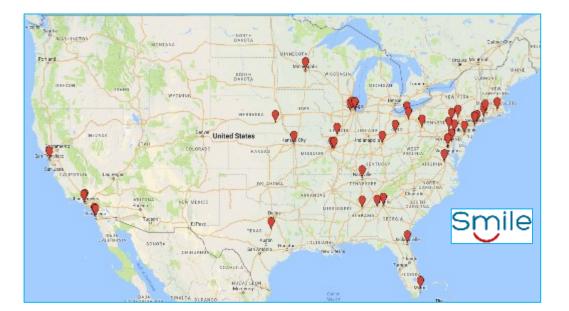
<u>Sensible Medical Innovations Lung fLuid</u> status monitor allows rEducing readmission rate of heart failure patients

NCT02448342

- > Post-FDA study for reimbursement and market adoption
- > Daily ReDS monitoring to guide treatment for reducing HF readmission rate
- > 43 US Sites
- > 268 Patients
 - > Stopped early planned for 380
 - > 135 ReDS patients

SMILE Clinical Trial

- > 133 SOC patients
- Follow-up 6.1 ± 3.4 months
- > Readmissions were collected and adjudicated by CEC





ReDS-guided Heart Failure Management



ReDS System



ReDS Cloud



ReDS Treatment Algorithm



- Focused electromagnetic RADAR beam through the right lung
- Absolute measurement of lung fluid content
- Normal lung measures 20-35% lung fluid content
- 90 seconds measurements and no skin contact

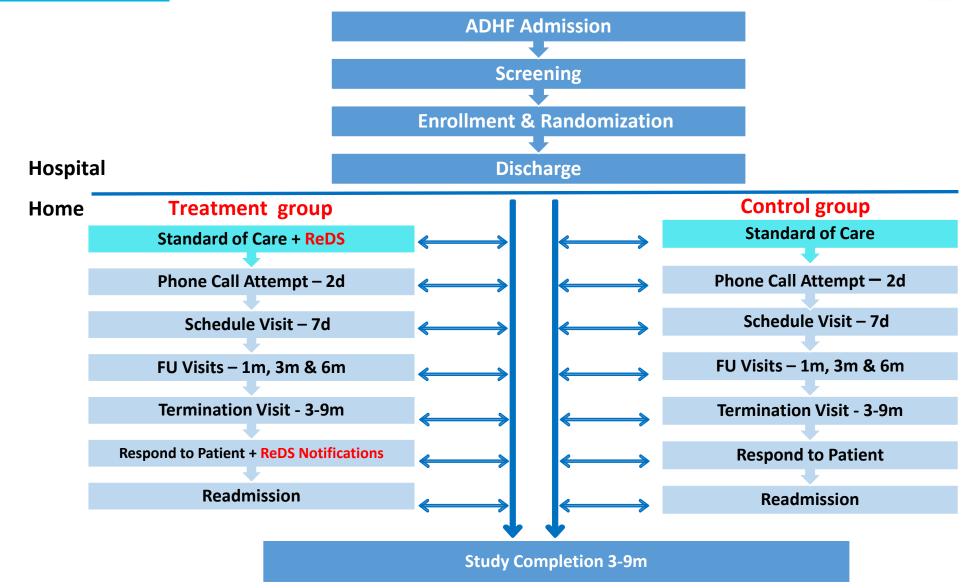
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- > Prospective, Randomized, Controlled, Multi-center Trial (open label)
- > ReDS-guided treatment vs. Standard of Care management
- > Methods:
 - > All patients:
 - > Enrollment during ADHF hospitalization or within 10 days following discharge
 - > ReDS patients:
 - > Daily ReDS measurements at home patients blinded to ReDS results
 - Readings sent to physicians using HIPAA-compliant dedicated cloud-based system; clinicians could log in and review readings at anytime
 - > Automatic Notifications were sent for out of range readings (default: 20-35%)
 - > Patients were to be treated according to a ReDS-guided treatment protocol

Study Flow







> Primary Efficacy Endpoint

> The rate of recurrent events of HF readmissions during entire follow-up period

Secondary Efficacy Endpoints

- > Time from discharge until the first event of HF readmissions through the entire follow-up period
- > Proportions of total days lost to hospitalization due to HF events
- > Time from discharge until all-cause mortality through entire follow-up period



- > Primary endpoint analyzed using the method of Anderson and Gill (A-G)
- ReDS-based-treatment (Modified ITT population) defined by
 - > No ReDS measurements for > 20 consecutive days, or
 - > No ReDS-guided treatment although > 8 threshold notifications sent
- > Robustness was confirmed by a Sensitivity and propensity matched analyses
 - Same propensity matching analysis was performed by CHAMPION due to FDA request to account for adherence

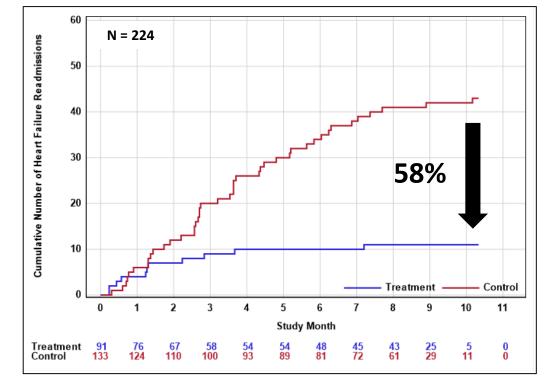
Patient Characteristics



Age (year) 69 (12) [35.1 92.3] 68 (13) [35.0 90.5] Male sex 95 (70%) 93 (70%) MMI (kg/m²) 29 (4) [20.4 37.1] 29 (4) NYHA LIJ, III, IV (%) (5.25,64,6) (2.25,63,10) ACC/AHA Heart Failure Stage C 112 (85%) 112 (84%) LVEF (≥40%) 41 (31%) 34 (27%) LVEF (≥40%) 41 (31%) 34 (27%) Number of Previous HF hospitlazation 3 (3) [0 15] 3 (2) [0 13] CRT-D 11 (8%) 12 (9%) CRT-P 1 (1%) 1 (1%) ICD 35 (26%) 39 (29%) Pacemaker 9 (7%) 13 (10%) Coronary artery disease 64 (49%) 62 (47%) Diabetes mellitus 71 (54%) 63 (247%) Diabetes mellitus 71 (54%) 63 (247%) Diabetes mellitus 71 (54%) 63 (247%) Chronic obstructive pulmonary disease 27 (20%) 30 (23%) Laboratory and hemodynamic analyses 27 (20%) 30 (23%) Creatinine (mg/dt) 1.5 (0.5) [0.6 3.0] 1			
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$\begin{array}{c c} CRT-D & 11 (8\%) & 12 (9\%) \\ CRT-P & 1 (1\%) & 1 (1\%) \\ ICD & 35 (26\%) & 39 (29\%) \\ Pacemaker & 9 (7\%) & 13 (10\%) \\ \hline Comorbidities \\ \\ Hypertension & 103 (78\%) & 100 (76\%) \\ Coronary artery disease & 64 (49\%) & 62 (47\%) \\ Diabetes mellitus & 71 (54\%) & 62 (47\%) \\ Diabetes mellitus & 71 (54\%) & 62 (47\%) \\ Atrial fibrillation & 65 (49\%) & 70 (53\%) \\ \hline Chronic obstructive pulmonary disease & 27 (20\%) & 30 (23\%) \\ \hline Laboratory and hemodynamic analyses \\ Creatinine (mg/dL) & 1.5 (0.5) [0.6 3.0] & 1.5 (0.5) [0.5 4.2] \\ GFR (mL/min per 1-73m^2) & 62 (26) [21 152] & 65 (31) [24 226] \\ Systolic blood pressure (mm Hg) & 121 (20) [83 183] & 118 (19) [81 173] \\ Diastolic blood pressure (mm Hg) & 68 (13) [37 104] & 70 (12) [44 95] \\ Heart rate (beats per min) & 75 (13) [44 111] & 78 (16) [48 144] \\ Prior Medications \\ Diuretic & 117 (86.7\%) & 120 (90.2\%) \\ Beta Blocker & 94 (69.6\%) & 108 (81.2\%) \\ Angiotensin-Converting Enzyme \\ Inhibitors & 39 (28.9\%) & 45 (33.8\%) \\ Angiotensin II Receptor Blockers & 13 (9.6\%) & 7 (5.3\%) \\ Angiotensin II Receptor Blockers & 13 (9.6\%) & 7 (5.3\%) \\ Hydralazine & 11 (8.1\%) & 12 (9.0\%) \\ Nitrate & 19 (14.1\%) & 18 (13.5\%) \\ If Channel Blocker & 7 (5.2\%) & 9 (6.8\%) \\ \end{array}$	Time from HF diagnosis (year)	6 (7) [0 47.7]	5 (6) [0 23.3]
CRT-P 1 (1%) 1 (1%) ICD 35 (26%) 39 (29%) Pacemaker 9 (7%) 13 (10%) Comorbidities	Number of Previous HF hospitlazation	3 (3) [0 15]	3 (2) [0 13]
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Atrial fibrillation 65 (49%) 70 (53%) Chronic obstructive pulmonary disease 27 (20%) 30 (23%) Laboratory and hemodynamic analyses 70 (53%) 70 (53%) Creatinine (mg/dL) 1.5 (0.5) [0.6 3.0] 1.5 (0.5) [0.5 4.2] GFR (mL/min per 1·73m²) 62 (26) [21 152] 65 (31) [24 226] Systolic blood pressure (mm Hg) 121 (20) [83 183] 118 (19) [81 173] Diastolic blood pressure (mm Hg) 68 (13) [37 104] 70 (12) [44 95] Heart rate (beats per min) 75 (13) [44 111] 78 (16) [48 144] Prior Medications Diuretic 117 (86.7%) 120 (90.2%) Beta Blocker 94 (69.6%) 108 (81.2%) Angiotensin-Converting Enzyme Inhibitors 39 (28.9%) 45 (33.8%) Angiotensin-Receptor Blockers 13 (9.6%) 7 (5.3%) Angiotensin-Receptor Neprilysin 9 (6.7%) 11 (8.3%) Hydralazine 11 (8.1%) 12 (9.0%) Nitrate 19 (14.1%) 18 (13.5%) 11 (9.0%) 18 (13.5%) 11 (6.3%)	Coronary artery disease	64 (49%)	62 (47%)
Chronic obstructive pulmonary disease 27 (20%) 30 (23%) Laboratory and hemodynamic analyses Creatinine (mg/dL) 1.5 (0.5) [0.6 3.0] 1.5 (0.5) [0.5 4.2] GFR (mL/min per 1·73m²) 62 (26) [21 152] 65 (31) [24 226] Systolic blood pressure (mm Hg) 121 (20) [83 183] 118 (19) [81 173] Diastolic blood pressure (mm Hg) 68 (13) [37 104] 70 (12) [44 95] Heart rate (beats per min) 75 (13) [44 111] 78 (16) [48 144] Prior Medications Diuretic 117 (86.7%) 120 (90.2%) Beta Blocker 94 (69.6%) 108 (81.2%) Angiotensin-Converting Enzyme Inhibitors 39 (28.9%) 45 (33.8%) Angiotensin-Receptor Blockers 13 (9.6%) 7 (5.3%) Angiotensin-Receptor Neprilysin 9 (6.7%) 11 (8.3%) 12 (9.0%) 11 (8.3%) Hydralazine 11 (8.1%) 12 (9.0%) Nitrate 19 (14.1%) 18 (13.5%) 19 (6.8%) 16 (6.8%)	Diabetes mellitus	71 (54%)	62 (47%)
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Angiotensin-Converting Enzyme Inhibitors 39 (28.9%) 45 (33.8%) Angiotensin II Receptor Blockers 13 (9.6%) 7 (5.3%) Angiotensin-Receptor Neprilysin 9 (6.7%) 11 (8.3%) Hydralazine 11 (8.1%) 12 (9.0%) Nitrate 19 (14.1%) 18 (13.5%) If Channel Blocker 7 (5.2%) 9 (6.8%)	Beta Blocker	94 (69.6%)	108 (81.2%)
Inhibitors 39 (28.9%) 45 (33.8%) Angiotensin II Receptor Blockers 13 (9.6%) 7 (5.3%) Angiotensin-Receptor Neprilysin 9 (6.7%) 11 (8.3%) Hydralazine 11 (8.1%) 12 (9.0%) Nitrate 19 (14.1%) 18 (13.5%) If Channel Blocker 7 (5.2%) 9 (6.8%)	Angiotensin-Converting Enzyme	· · ·	· · · ·
Angiotensin-Receptor Neprilysin 9 (6.7%) 11 (8.3%) Hydralazine 11 (8.1%) 12 (9.0%) Nitrate 19 (14.1%) 18 (13.5%) If Channel Blocker 7 (5.2%) 9 (6.8%)		39 (28.9%)	45 (33.8%)
Angiotensin-Receptor Neprilysin 9 (6.7%) 11 (8.3%) Hydralazine 11 (8.1%) 12 (9.0%) Nitrate 19 (14.1%) 18 (13.5%) If Channel Blocker 7 (5.2%) 9 (6.8%)	Angiotensin II Receptor Blockers	· · · · ·	
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If Channel Blocker 7 (5.2%) 9 (6.8%)		· · · · ·	
		· · ·	· · · · · · · · · · · · · · · · · · ·
	Digoxin	14 (10.4%)	18 (13.5%)

SMILE - Home Monitoring RCT





Presented by Dr. W. T. Abraham at HFSA, Philadelphia, Sep 2019

N = 224	Treatment (N=91)	Control (N=133)	HR	p-value	95% CI
Number of HF Readmissions	11	43	0.42	p = 0.01	[0.22-0.82]

> Statistical analysis: Anderson and Gill method

Modified ITT population defined by

- > No ReDS measurements for > 20 consecutive days
- No ReDS-guided treatment although > 8 threshold notifications sent
- Propensity analysis showed robustness of results
 - > HR = 0.34, 95% CI [0.17-0.68], P = 0.002
- Note: since study was stopped early traditional ITT was not powered

ReDS-guided HF management when used as intended resulted in a significant 58% reduction in recurrent ADHF hospitalizations

SMILE Study Modified ITT Secondary Endpoint Results



Time to First HF Readmission

N = 224	Treatment (N=91)	Control (N=133)	HR	95% CI	p-value
Number of HF	10	34	0.51	0.25-1.03	n = 0.06
Readmissions	10	54	0.51	0.25-1.05	p = 0.06

Proportion of Total Days Lost to HF Hospitalization

N = 224	Treatment (N=91)	Control (N=133)	Reduction	p-value
Proportion Total Days				
Lost to Hospitalization	0.6%	1.1%		
Due to HF Events (%)				
Average Per Patient	1.02	2.06	50.4%	p = 0.02
(days)	1.02	2.00	50.470	p = 0.02

Mortal	it
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ty	N = 224	Treatment (N=91)	Control (N=133)	p-value
	All-cause Mortality	7	9	N.S.
	CV Mortality	2	5	N.S.

Modified ITT Sensitivity Analysis



Patient non-adherence	Non-adherence to ReDS-guided Protocol	Efficacy	p-value
No ReDS measurements for X consecutive days	No ReDS-guided treatment although more than X notifications were sent	HR	
>20 days	>4 notifications	0.43	0.01
>20 days	>8 notifications	0.42	0.01
>20 days	>16 notifications	0.45	0.02
>14 days	>4 notifications	0.45	0.02
>14 days	>8 notifications	0.44	0.01
>14 days	>16 notifications	0.47	0.02
>10 days	>4 notifications	0.48	0.03
>10 days	>8 notifications	0.47	0.03
>10 days	>16 notifications	0.51	0.04

Combinations of 10, 14 & 20 days with 4, 8 & 16 notifications show similar results: HR is between 0.42 to 0.51 --> 49% to 58% statically significant reduction in HF readmissions

Modified ITT Propensity Matched Analysis



- > Propensity scores were produced using baseline measures
- > Nearest neighbor matching was used to identify a SOC group which was matched 1:1 with the modified ITT group to account for any baseline differences between the populations
- For completeness of the propensity model, all of the following baseline measures were included in the model:
 - > Age
 - > Gender
 - > Race (White/Non-white)
 - > Weight
 - Body Mass Index
 - > Respiratory rate
 - > HF etiology

- History of CAD
- > Diabetes Mellitus
- > HFrEF vs. HFpEF
- > ACC/AHA Stage A, B vs. C, D
- > NYHA Class 1, 2 vs. 3, 4
- > Time from HF diagnosis
- > # of previous HF hospitalizations



The rate of recurrent events of HF readmissions during entire follow-up period (using A-G model)

N = 182	Treatment N=91	Control N=91	HR	p-value	95% CI
Number of HF Readmissions	11	36	0.34	0.002	0.17-0.68





>422 reported Adverse Events

> 87 were reported as Serious AEs

> None of the Adverse Events were related to the use of the Device

- > 5 *possibly* related
 - > 4 AKI, 1 near Syncope
- > 4 unlikely related
 - > 3 Falls, 1 asymptomatic orthostatic hypotension



> ReDS arm patients filled satisfaction questionnaire

> The ReDS system got an average score of 4.5/5 in patient satisfaction

	Score 1-5
PSQ Questions - Scores range from 5 (strongly agree) to 1 (strongly disagree)	Treatment (N=135)
1. I am able to put the SensiVest on by myself.	4.7 ± 0.9 (92)
I was able to operate the SensiVest after one training session.	4.6 ± 1.0 (91)
3. I understood the training materials.	4.7 ± 0.8 (92)
4. The SensiVest is easy to use.	4.7 ± 0.8 (93)
5. The SensiVest worked reliably during the study.	4.4 ± 0.9 (92)
6. The SensiVest made me feel safer at home.	4.5 ± 0.9 (88)
7. The SensiVest saved me a trip to the hospital.	4.4 ± 1.2 (86)
8. The SensiVest saved me several trips to the hospital.	4.3 ± 1.1 (84)
9. I am more involved in my care when using the SensiVest.	4.3 ± 1.2 (90)
10. I learned more about my disease when using the SensiVest.	4.1 ± 1.2 (87)
11. I feel better about my health when I use the SensiVest.	4.4 ± 1.1 (91)
12. The call center is helpful.	4.5 ± 1.0 (86)
13. My doctor/NP can get a good understanding of my medical problem when I use the SensiVest.	4.7 ± 0.7 (90)
14. My doctor/NP uses information from the SensiVest during visits or telephone follow-ups.	4.8 ± 0.6 (86)
15. My doctor/NP used the information from the SensiVest to adjust my treatment and medications	4.5 ± 0.9 (85)
16. I would like to use the SensiVest in the future.	4.2 ± 1.3 (92)
17. I would recommend the SensiVest to other patients with the same medical condition.	4.6 ± 0.9 (92)
18. I feel more confident being active because I have a SensiVest.	4.1 ± 1.2 (88)
19. I like to be responsible of my own health.	4.8 ± 0.6 (91)
20. I like to take care of myself.	4.9 ± 0.5 (92)
Cells contain mean ± SD (N)	

Score 1-5