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Supplemental Appendix 1
TiME Trial Data and Safety Monitoring Board

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Supplemental Table 1. Demonstration Project Objectives.

Partner with multiple health systems and leverage their clinical care infrastructures to conduct a large trial embedded in care delivery
Address regulatory and ethical considerations for waiving informed consent
Use a single IRB of record to oversee hundreds of study sites without local investigators
Enroll a cohort of patients incident to dialysis with demographic and clinical characteristics representative of the overall US hemodialysis population
Harmonize highly granular clinical data from hundreds of study sites and multiple health systems and achieve a high degree of data completeness
Monitor trial enrollment, fidelity to the intervention, and safety using an efficient centralized approach
Determine whether facility adoption of a default session duration of >4 hours for thrice weekly hemodialysis improves clinical outcomes

Supplemental Table 2. Approaches to Assessing Facility Suitability Prior to Enrollment and Engaging Clinical Personnel and Patients Prior to and During the Trial

Activity	Trial Phase	Provider of Activity	Target for Engagement	Purpose
Nephrologist survey	During trial design	Dialysis provider organization	Nephrologists	Obtain feedback from nephrologists about the planned trial intervention
Informational sessions group conference calls	Prior to facility enrollment	Research team[a]	Regional Administrators	Introduce the purpose of the trial and facility responsibilities to potential facility participants
Informational brochure	Prior to facility enrollment	Research team[a]	Dialysis facility medical and administrative leadership and nephrologists	Provide purpose of trial, responsibilities of facility and nephrologist
Letter from NIDDK/NIH	Prior to facility enrollment	Trial sponsor (NIDDK)	Dialysis facility medical and administrative leadership and nephrologists	Provide potential participating facilities with NIDDK view of importance of trial
Informational web video	Prior to facility enrollment	Research team[a]	Dialysis facility medical, nursing, and administrative leadership	Introduce the purpose of the trial and facility responsibilities to potential facility participants
Facility commitment form	Prior to facility enrollment	Research team[a]	Dialysis facility medical, nursing, and administrative leadership	Document willingness of facility personnel to implement the trial intervention
Review and modeling of facility capacity for longer treatments	Prior to facility enrollment	Dialysis provider organizations	Dialysis facility medical, nursing, and administrative leadership	Assess suitability of dialysis unit for trial participation
In-person informational meetings at national nephrology scientific meeting	Prior to enrollment	Research team[a]	Nephrologists	Provide information to nephrologists considering participation in trial
Training web video	After facility enrollment; prior to trial launch	Research team[a]	Dialysis facility medical, nursing, and administrative leadership	Provide on-line training for trial implementation
"Frequently Asked Questions" Document	During trial conduct	Research team[a]	Dialysis facility nephrologist and nursing staff	Provide information to aid trial implementation
Reviewed performance of the first 5 Intervention facilities enrolled to inform the approach with subsequent facilities[b]	During initial period of trial conduct	Research team[a]	Not applicable	Evaluate processes and implementation of the intervention before the full roll-out of the trial[b]
Trial poster	During trial conduct	Research team[a]	Patients and facility staff	Provide patients and facility personnel with information throughout duration of the trial
Letter from Dialysis Providers' Chief Medical Officer	During trial conduct	Dialysis provider organizations	Patients and facility staff	Provide facility personnel with dialysis provider organization view of importance of trial
Refresher webinars	During trial conduct	Research team[a]	Dialysis facility medical, nursing, and administrative leadership	Provide facility personnel with purpose of the trial and tips for implementing the intervention

Activity	Trial Phase	Provider of Activity	Target for Engagement	Purpose
Facility performance reports	During trial conduct	Research team[a]	Dialysis facility medical, nursing, and administrative leadership	Review facility performance implementing intervention, discuss challenges and propose solutions
Patient newsletters	During trial conduct	Research team[a]	Patients	Update patients on trial progress and purpose
Facility newsletters	During trials conduct	Research team[a]	Facility staff	Update participating facilities on trial progress and provide tips for implementing the intervention
Recruitment of dialysis provider organization's regional medical directors to serve as trial champions	During trial conduct	Dialysis provider organization	Facility nephrologists and staff	Interact with participating facilities leveraging existing relationships to encourage intervention implementation and troubleshoot challenges
Informational booth at national nephrology scientific meeting and at dialysis provider annual medical director meetings	During trial conduct	Research team[a]	Nephrologists	Publicize the trial and obtain input about implementation experience and challenges
Scheduled teleconforerences	During trial conduct	Research team[a]	Facility multidisciplinary care team (intervention facilities)	Review facility performance implementing intervention, discuss challenges and propose solutions
Trial notepads and pens	During trial conduct	Research team[a]	Patients and facility staff	Publicize the trial to patients and facility staff
Pilot financial incentive program[c]	During trial conduct	Research team[a]	Patients and facility staff	Determine whether financial incentives improve uptake of the intervention sufficiently to justify a study-wide incentive program

[a]Research team includes investigators and project personnel at the academic centers and the dialysis provider organizations

[b]During the first 2 months of the trial the mean delivered session durations at the first 5 Intervention facilities (15 patients, 376 sessions) were: 253, 262, 269, 252, and 241 minutes, respectively.

[c]During the conduct of the trial, the investigative team performed pilot testing of financial incentives for patients and facilities to improve adherence to the trial intervention. Because of insufficient response to the incentives during the pilot testing, the program was not advanced to a full-scale program.

Supplemental Table 3. Sample Size Determination

	Enrollment mos/Total Study mos	# Clusters	SD for Cluster Size (1° Analysis Population)	Annual Loss to F/U	Annual Mortality	ICC for Mortality	Sample Size 1° Analysis Population	Sample Size Full Analysis Population	Power to detect HR 0.85
Pre-Trial Assumptions	12/36	402	0	5%	18%	0.03	4020	6432	80%
Revised Assumptions During Trial	36/54	256[1]	10	10%	18%	0.015	4250	6800	80%
	36/54	256[1]	16	10%	18%	0.015	4250	6800	77%
	36/54	256[1]	10	10%	18%	0.012	4250	6800	82%
	36/54	256[1]	16	10%	18%	0.012	4250	6800	80%
Observed Values at End of Trial	36/40	256[1]	12.5	7.7%	19.5%	0.008	4470	7035	84.3%

[1]266 facilities were randomized and 10 facilities withdrew prior to enrolling participants.

Supplemental Table 4. Mortality Risk with Adjustment for Baseline Characteristics

	Hazard Ratio (95% CI)	
	Primary Analysis Population	**Full Analysis Population**
Intervention vs Usual Care[1]	0.97 (0.84, 1.12)	0.97 (0.85, 1.12)
Intervention vs Usual Care with Adjustment for Baseline Charactersitics[2]	1.04 (0.91, 1.19)	1.00 (0.88, 1.14)

[1]Adjusted for dialysis provider organization and facility

[2]Adjusted for sex, race, age, body mass index, cardiac disease, diabetes, serum albumin, central venous catheter use, dialysis provider organization and facility

Supplemental Table 5a. Relative Contributions of Sources of Variation to Total Variance in Prescribed Session Duration

Randomized Assignment	Nested Source of Variation	Variance Components as a Proportion of Total Variance[a]				
		<210 minutes	210 - <225 minutes	225 - <240 minutes	240 - <255 minutes	≥255 minutes
Intervention	Dialysis Provider	0.003	0.005	0.002	0.014	0.000
	Facility	0.073	0.084	0.014	0.074	0.260
	Patient	0.665	0.613	0.534	0.602	0.501
	Dialysis Session	0.260	0.298	0.500	0.310	0.239
Usual Care	Dialysis Provider	0.041	0.044	0.024	0.050	0.020
	Facility	0.120	0.060	0.023	0.115	0.044
	Patient	0.622	0.621	0.527	0.576	0.665
	Dialysis Session	0.217	0.274	0.425	0.260	0.271

[a]The total variance within each session duration category was divided into the four depicted nested clusters and analyzed by a random effects model with a completely nested design.

Randomized Assignment	Number of Dialysis Sessions	Proportion of Sessions with Ordered Session Duration				
		<210 minutes	210 - <225 minutes	225 - <240 minutes	240 - <255 minutes	≥255 minutes
Intervention	499696	0.160	0.275	0.092	0.237	0.235
Usual Care	639071	0.237	0.302	0.090	0.300	0.070

Supplemental Table 5b. Relative Contributions of Sources of Variation to Total Variance in Delivered Session Duration

Randomized Assignment	Nested Source of Variation	Variance Components as a Proportion of Total Variance[a]				
		<210 minutes	210 - <225 minutes	225 - <240 minutes	240 - <255 minutes	≥255 minutes
Intervention	Dialysis Provider	0.003	0.004	0.0046	0.010	0.000
	Facility	0.051	0.064	0.0093	0.046	0.181
	Patient	0.443	0.415	0.270	0.398	0.390
	Dialysis Session	0.503	0.517	0.716	0.546	0.429
Usual Care	Dialysis Provider	0.024	0.034	0.027	0.033	0.016
	Facility	0.103	0.044	0.015	0.084	0.033
	Patient	0.440	0.427	0.267	0.407	0.477
	Dialysis Session	0.433	0.495	0.691	0.476	0.475

[a]The total variance within each session duration category was divided into the four depicted nested clusters and analyzed by a random effects model with a completely nested design.

Randomized Assignment	Number of Dialysis Sessions	Proportion of Sessions with Delivered Session Duration				
		<210 minutes	210 - <225 minutes	225 - <240 minutes	240 - <255 minutes	≥255 minutes
Intervention	499696	0.240	0.246	0.111	0.209	0.194
Usual Care	639071	0.314	0.267	0.113	0.238=	0.068

Supplemental Table 6. Facility-Reported Reasons for Not Implementing Intervention Session Duration

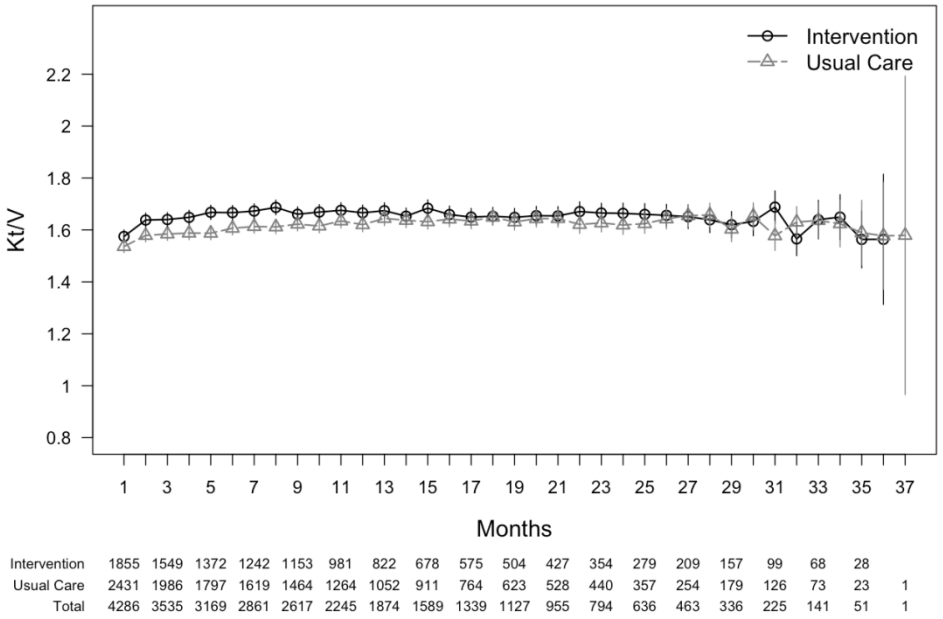
Reason	N (%)
Patient refused	55 (37.2)
Medically unnecessary per nephrologist	24 (16.2)
Medical contraindication per nephrologist	12 (8.1)
Death prior to implementation	3 (2.0)
Transportation issue	3 (2.0)
Reason unknown	50 (33.8)

[a]Facility nurse managers asked during trial conduct to provide specific reason for patient not meeting intervention target (sample of 148 patients)

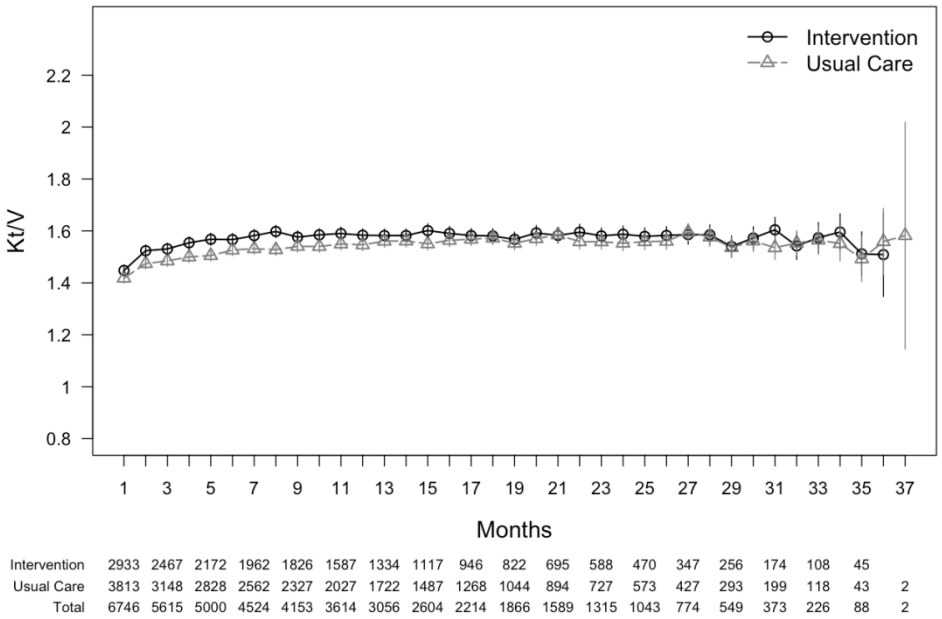
Supplemental Table 7. Facility-Reported Challenges Implementing the Intervention[a]

Patient resistance to longer treatments
Nephrologist concern about burden to patients
Nephrologist view that longer time is not beneficial to small patients or patients with Kt/V (indicator of small solute clearance) meeting clinical target
Nephrologist concern that patients will transfer to other facilities
Staff concerns about impact of longer sessions on work flow

[a]Qualitative information provided by multidisciplinary care team members during teleconferences conducted during trial conduct



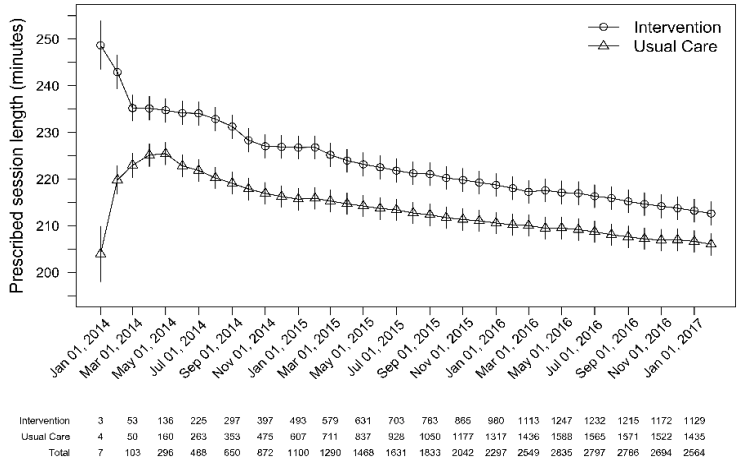
A. Primary Analysis Population



B. Full Analysis Population

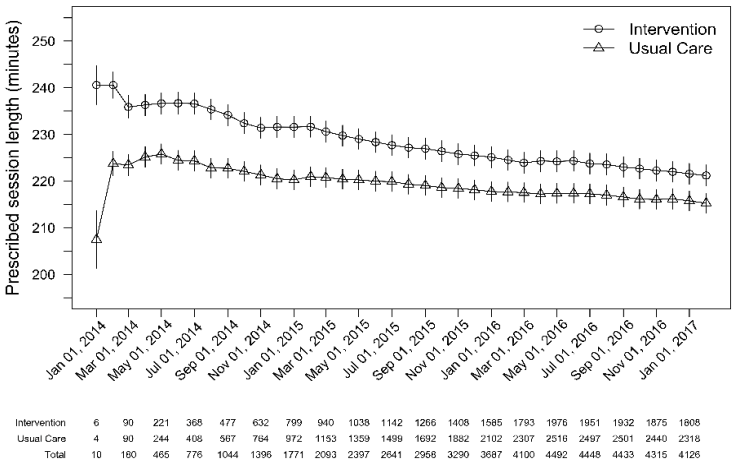
Supplemental Figure 1. Dialysis session single-pool Kt/V as an indicator of dialytic urea clearance. K represents the rate of urea clearance by the dialyzer in milliliters per minute, t the duration of the treatment session in minutes, and V the volume of distribution of urea in the patient in milliliters[1]. Kt/V is typically determined once per month. The values shown are means with 95% CIs. Estimated Kt/V values were calculated using linear mixed effects models to account for both participants within the same facility and repeated measurements within the same participant. A. Primary analysis population (patients with Watson volume ≤42.5 liters). B. Full analysis population (all patients).

[1]Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J. Am. Soc. Nephrol.* 1993;4(5):1205-1213



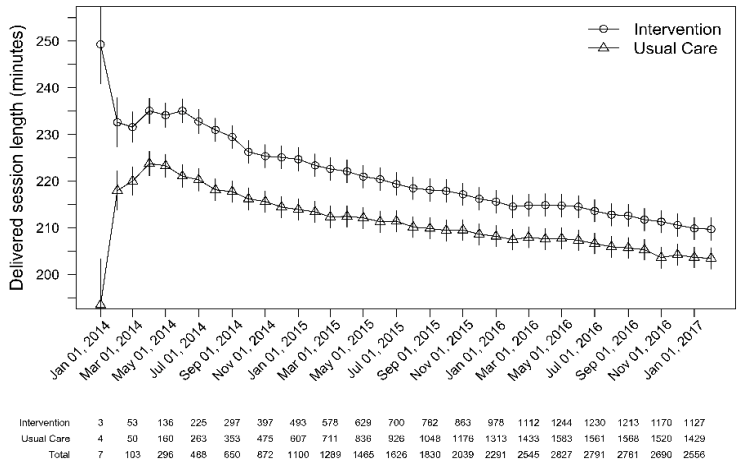
Intervention	3	53	136	225	297	397	493	579	631	703	783	865	980	1113	1247	1232	1215	1172	1129
Usual Care	4	50	160	263	353	475	607	711	837	928	1050	1177	1317	1436	1588	1565	1571	1522	1435
Total	7	103	296	488	650	872	1100	1290	1468	1631	1833	2042	2297	2549	2835	2797	2786	2694	2564

A. Primary Analysis Population



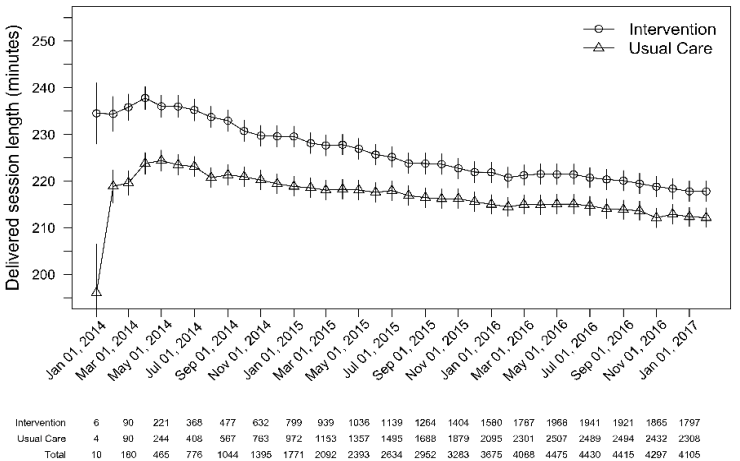
Intervention	6	90	221	368	477	632	799	940	1038	1142	1266	1408	1585	1793	1976	1951	1932	1875	1808
Usual Care	4	90	244	408	567	764	972	1153	1359	1499	1692	1882	2102	2307	2516	2497	2501	2440	2318
Total	10	180	465	776	1044	1396	1771	2093	2397	2641	2958	3290	3687	4100	4492	4448	4433	4315	4126

B. Full Analysis Population



Intervention	3	53	136	225	297	397	493	578	629	700	782	863	978	1112	1244	1230	1213	1170	1127
Usual Care	4	50	160	263	353	475	607	711	836	926	1048	1176	1313	1433	1583	1561	1568	1520	1429
Total	7	103	296	488	650	872	1100	1289	1465	1626	1830	2039	2291	2545	2827	2791	2781	2690	2556

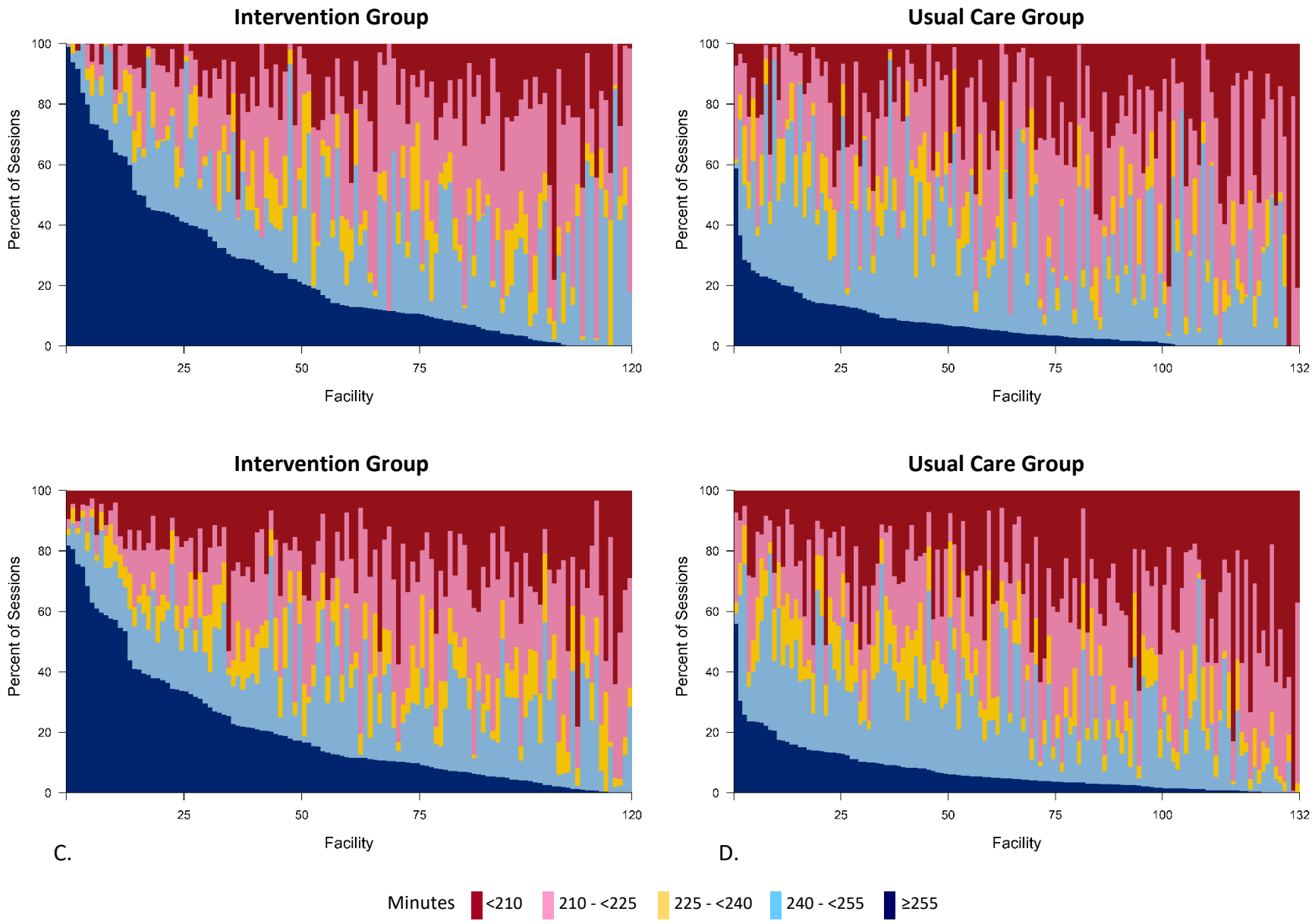
C. Primary Analysis Population



Intervention	6	90	221	368	477	632	799	939	1036	1139	1264	1404	1580	1787	1968	1941	1921	1865	1797
Usual Care	4	90	244	408	567	763	972	1153	1357	1495	1688	1879	2095	2301	2507	2489	2494	2432	2308
Total	10	180	465	776	1044	1395	1771	2092	2393	2634	2952	3283	3675	4088	4475	4430	4415	4297	4105

D. Full Analysis Population

Supplemental Figure 2. Hemodialysis session duration over calendar-time. The value shown at each month represents the per-participant mean value and 95% CIs over the preceding 30 days. Estimated session durations and their slopes were calculated using linear mixed effects models to account for both participants within the same facility and repeated measurements within the same participant. A. Prescribed session duration for the primary analysis population (patients with Watson volume ≤42.5 liters); slope -0.71 for Intervention group; slope -0.52 for Usual Care group (p=0.04 for difference). B. Prescribed session duration for the full analysis population (all patients); slope -0.43 for Intervention group; slope -0.16 for Usual Care group (p<0.001 for difference). C. Delivered session duration for the primary analysis population (patients with Watson volume ≤42.5 liters); slope -0.83 for Intervention group; slope -0.64 for Usual Care group (p<0.001 for difference). D. Delivered session duration for the full analysis population (all patients); slope -0.59 for Intervention group; slope -0.39 for Usual Care group (p<0.001 for difference)



Supplemental Figure 3. Distribution of session durations by facility for the full analysis population (all patients). Facilities are ordered along the X axis based on the percentage of sessions ≥4.25 hours throughout follow-up. A. Prescribed session durations for the Intervention facilities. B. Prescribed session durations for the Usual Care facilities. C. Delivered session durations for the Intervention facilities. D. Delivered session durations for the Usual Care facilities.