Title: Three week compared to seven week run-in period length and the assessment of pre-randomization adherence: a study within a trial

Running head: Run-in period length and adherence

Number of words: 2769

Authors:

David Collister[a,b,c] (DC)
Affiliation:
a) Population Health Research Institute
b) Department of Health Research Methods, Evidence and Impact, McMaster University
c) Department of Medicine, McMaster University
Address:
237 Barton Street East, Population Health Research Institute, Hamilton, Canada, L8L 2X2
Email: dtcollister@gmail.com

Lawrence Mbuagbaw (LM)
Afilliation:
b) Department of Health Research Methods, Evidence and Impact, McMaster University
Address:
3rd floor Marian Wing, St. Joseph's Healthcare Hamilton, 50 Charlton Avenue East, Hamilton, Canada, L8N 4A6
Email: mbuagblc@mcmaster.ca

Gordon Guyatt[b,c] (GG)
Affiliation:
b) Department of Health Research Methods, Evidence and Impact, McMaster University
c) Department of Medicine, McMaster University
Address:
1280 Main Street West, Hamilton, Canada, L8S 4L8
Email: guyatt@mcmaster.ca

PJ Devereaux[a,b,c] (PJD)
Affiliation:
a) Population Health Research Institute
b) Department of Health Research Methods, Evidence and Impact, McMaster University
c) Department of Medicine, McMaster University
Address: 237 Barton Street East, Population Health Research Institute, Hamilton, Canada, L8L 2X2
Email: PJ.Devereaux@phri.ca

Karthik K. Tennankore[d] (KKT)
Affiliation:
d) Division of Nephrology, Department of Medicine, Dalhousie University
Address:
5081 Dickson Building, 5820 University Avenue, Nova Scotia Health Authority, Halifax, Canada
Email: karthikk.tennankore@nshealth.ca

Gilmar Reis[e] (GR)
Affiliation:
e) Departamento de Medicina, Pontifícia Universidade Católica de Minas Gerais
Address:
R. Domingos Viêira, 300 - Sala 606 - Santa Efigênia, Belo Horizonte - MG, 30150-240, Brazil
Email: administrador@cardresearch.org

Laura Sola[f] (LS)
Affiliation:
f) CASMU-IAMPP
Address:
Av. Rivera 4437, Montevideo 11400, Uruguay
Email: lsola@casmu.com

Denis Xavier[g] (DX)
Affiliation:
g) Department of Pharmacology and Division of Clinical Research, St. John's Medical College
Address:
St. John's Research Institute, St. John's National Academy of Health Sciences, Bangalore - 560 034 Karnataka, India
Email: denis.xavier@stjohns.in

Vivekanand Jha[h] (VJ)
Affiliation:
h) The George Institute for Global Health (New Delhi, India)
Address:
311-312, Third Floor, Elegance Tower, Plot No. 8, Jasola District Centre, New Delhi 110025 India
Email: vjha@georgeinstitute.org.in

Martin Gallagher[i] (MG)
Affiliation:
i) The George Institute for Global Health (Sydney, Australia)
Address:
The George Institute for Global Health, Level 5, 1 King Street, Newtown NSW 2042 Australia
Email: mgallagher@georgeinstitute.org.au

Antonio L. Dans[j] (ALD)
Affiliation:
j) University of the Philippines College of Medicine
Address:
Pedro Gil Street, Taft Ave, Ermita, Manila, 1000 Metro Manila, Philippines
Email: aldans@up.edu.ph

Wen Liu[k] (WL)
Affiliation:
k) Hospital Sultanah Aminah
Address:
Hospital Sultanah Aminah, Johor Bahru, Johor 80100, Malaysia

Email: plnjl@yahoo.com

Janak de Zoysa[l] (JdZ)
Affiliation:
l) Department of Medicine, The University of Auckland, Auckland, New Zealand
Address:
Department of Medicine, The University of Auckland, Private Bag 92019, Auckland, New Zealand
Email: Janak.deZoysa@waitematadhb.govt.nz

Camilo Félix[m] (CF)
Affiliation:
m) Facultad de Ciencias Medicas Eugenio Espejo, Universidad Tecnológica Equinoccial,
Address:
Facultad de Ciencias Medicas Eugenio Espejo, Universidad Tecnológica Equinoccial, Quito, Ecuador, Sede Santo Domingo, Vía Chone, Km 4 ½
Email: camilofelix.achieve@gmail.com

Patrick B Mark[n] (PBM)
Affiliation:
n) Institute of Cardiovascular and Medical Sciences
Address:
Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Pl, Glasgow, United Kingdom G12 8TA
Email: patrick.mark@glasgow.ac.uk

Zuo Li[o] (ZL)
Affiliation:
o) Department of Nephrology, Peking University People's Hospital, Beijing, China
Address:
11 Xizhimen S St, Xicheng District, Beijing, China
Email: ZuoLiMD@hotmail.com

Jessica Tyrwhitt[a] (JT)
Affiliation:
a) Population Health Research Institute
Address:
237 Barton Street East, Population Health Research Institute, Hamilton, Canada, L8L 2X2
Email: Jessica.Tyrwhitt@phri.ca

Joanne Wilkinson[a] (JW)
Affiliation:
a) Population Health Research Institute
Address:
237 Barton Street East, Population Health Research Institute, Hamilton, Canada, L8L 2X2
Email: Joanne.Wilkinson@phri.ca

Patrick Sheridan[a] (PS)
Affiliation:
a) Population Health Research Institute

Address:
237 Barton Street East, Population Health Research Institute, Hamilton, Canada, L8L 2X2
Email: Patrick.Sheridan@phri.ca

Fei Yuan[a] (FY)
Affiliation:
a) Population Health Research Institute
Address:
237 Barton Street East, Population Health Research Institute, Hamilton, Canada, L8L 2X2
Email: Fei.Yuan@phri.ca

Michael Walsh (MW)
Affiliation:
a) Population Health Research Institute
b) Department of Health Research Methods, Evidence and Impact, McMaster University
c) Department of Medicine, McMaster University
Address:
237 Barton Street East, Population Health Research Institute, Hamilton, Canada, L8L 2X2
Email: lastwalsh1975@gmail.com

On behalf of the ACHIEVE investigators*

Corresponding author:
David Collister
Email: dtcollister@gmail.com
Phone: 905-522-1155 extension 34796
Address: 237 Barton Street East, Population Health Research Institute, Hamilton, Canada, L8L 2X2
Present phone: 204-632-632-3664
Present address: Chronic Disease Innovation Center, 2300 McPhillips Street, Winnipeg, Canada, R2V 3M3

Trial registration: ClinicalTrials.gov Identifier: NCT03020303

Abstract and key words:

Background/Aims: To examine how measuring adherence at 3 weeks by self-report and pill counts compares to measurements at 7 weeks in a pre-randomization run-in period.

Methods: Study within a trial of an international parallel group randomized controlled trial (RCT) that compares spironolactone to placebo. Adults receiving dialysis enter an 8-week active run-in period with spironolactone. Adherence was assessed by both self-report and pill counts in a subgroup of participants at both 3 weeks and 7 weeks.

Results: 332 participants entered the run-in period of which 166 had complete data. By self-report, 146/166 (94.0%) and 153/166 (92.2%) had at least 80% adherence at 3 and 7 weeks respectively (kappa = 0.27 (95% C.I. 0.16 to 0.38). By pill counts, the mean (SD) adherence was 96.5% (16.1%) and 92.4% (18.2%) at 3 and 7 weeks respectively (r=0.32) with a mean (SD) difference of 3.1% (17.8%) and a 95% limit of agreement from -31.7% to +37.9%. The proportion of adherent participants by self-report and pill counts at 3 weeks agreed in 87.4% of participants (McNemar's p-value 0.58, kappa 0.11, p=0.02) and at 7 weeks agreed in 92.2% (McNemar's p-value 0.82, kappa 0.47, p<0.001).

Conclusions: Three and seven-week run-in periods and both self-reported and pill count assessments performed similarly.

Key words: study within a trial, run-in period, adherence, dialysis

Abstract word count: 205

Introduction:

Run-in periods are pre-randomization study procedures frequently used to better select participants for randomized controlled trials (RCTs). They may involve the use of active study drug or placebo and may serve a variety of purposes. One specific use is to assess participant adherence for eligibility to ensure included participants are likely to take study treatments as prescribed. Other reasons for run-in periods include to standardize background therapy, exclude participants with intolerance or to select for responders(1, 2). Run-in periods that assess participant adherence can improve adherence in RCTs and thereby enhance statistical power(3). However, their optimal design is uncertain with regards to their duration and procedures(4, 5). The duration of a run-in period is important because longer run-in periods may better identify adherent participants than shorter run-in periods which may further improve statistical power but at the trade-off of increasing trial duration, possible redundancy, complexity and costs. Similarly, whether the simple method of assessing adherence by self-report identifies adherent participants to a similar degree of the more laborious method of assessing adherence by pill counts is also uncertain.

A Study Within A Trial (SWAT) is a study embedded in a RCT that evaluates its procedures in order to determine how to best conduct the trial with regards to recruitment, retention or other issues(6). We performed a SWAT of the Aldosterone bloCkade for Health Improvement EValuation in End-stage renal disease (ACHIEVE) trial which uses an active run-in period to identify adherent participants able to tolerate the drug spironolactone without hyperkalemia. We compared adherence at 3 weeks and 7 weeks assessed by self-report and pill counts to determine the extent to which adherence at 3 weeks differs from 7 weeks and the extent to which self-reported adherence differs from that measured by pill counts.

Materials and Methods:

Summary of the ACHIEVE trial

ACHIEVE is an international parallel group RCT comparing spironolactone 25 mg once daily to placebo in at least 2750 participants(7). The primary objective of ACHIEVE is to determine if spironolactone reduces cardiovascular (CV) morbidity and mortality in patients receiving chronic dialysis. The primary outcome is a composite of CV death and hospitalization for heart failure. Its inclusion criteria for participants are 1) age ≥45 years or age ≥18 years with diabetes mellitus; 2) on dialysis >90 days; 3) on either hemodialysis prescribed at least 2 treatments per week or peritoneal dialysis prescribed with at least 1 exchange daily; and 4) able to provide informed consent. Its eligibility criteria are designed to test the intervention in a maximally representative compliant dialysis population at risk of CV morbidity and mortality in whom the intervention is safe. Participants with history of recent hyperkalemia (K+>5.8mmol/L) or hyperkalemia during the active run-in period (K+>6.0mmol/L) are excluded. All participants provided written informed consent.

Open label active run-in period in ACHIEVE

Potentially eligible participants receive spironolactone 25 mg (1 tablet) by mouth once daily for at least 8 weeks (extended up to 98 days as each run-in period bottle contains 100 tablets). Adherence is assessed at 7 weeks by self-report in all participants to determine their eligibility for randomization. Participants with serum potassium measurements ≤6.0 mmol/L who tolerate spironolactone, take ≥80% of the run-in study drug measured by self-report, and still provide consent are randomized.

Additional adherence monitoring during the run-in period

ACHIEVE began recruitment in 2017. In a subgroup of participants, we added an optional study visit as determined by local investigators at 3 weeks (window 14 to 35 days) for additional adherence monitoring by self-report and pill counts. Participants identified as non-adherent at 3 weeks were counseled to continue taking their study medication but were not excluded at that time. The degree of adherence by self-report was classified as <50%, 50-79%, or ≥80%. The difference between the 100 dispensed tablets and those remaining at a visit (counted by a research coordinator or investigator) were considered the pill count and this number was divided by the number of days since starting the study medication to compute the percentage of pills used. We evaluated the run-in duration after 1000 participants were recruited.

Statistical Analysis

Descriptive statistics using means (standard deviation [SD]) or medians (25^{th} to 75^{th} percentile [IQR]) for continuous data and percentages for categorical data were used to summarize data. The degree of adherence by pill counts was calculated as [(100 - the number of pills left in the study bottle)/the number of days at the study visit since entering the run-in period] x 100%. Adherence was defined as self-reported adherence of ≥80% and as a pill count ≥80%. Adherence was also categorized as <50%, 50<80% and ≥80% by self-report and pill count. A complete case analysis was performed without imputation of any missing values.

The agreement between self-reported adherence and that measured by pill counts was assessed at each of 3 and 7 weeks by calculating the kappa coefficient (k). The agreements of the 3-week assessments with the 7-week assessments were assessed with Pearson's correlation and a Bland-Altman plot coefficient for pill counts. McNemar's test for paired proportions for categories of adherence (<80% or ≥80%) was performed for both self-reported adherence and that measured by pill counts in addition to

calculating the kappa coefficient. We performed a sensitivity analysis that used adherence categorized as <80% and ≥80% for both self-reported adherence and pill counts and calculated the phi coefficient (φ) due to the difficulty in achieving moderate and high kappas at extremes of distributions. We also performed another sensitivity analysis for patients with missing data due to sites not completing 3 week study visits or missing pill counts as they were not mandatory study procedures.

Assuming a 0.4 correlation between paired observations and an adherence of 85% at 8 weeks (based on pilot work), assessing adherence in 166 participants with paired 3 and 7 week assessments allowed 80% power to detect at least a 10% difference in adherence with a two-sided alpha of 0.05 using McNemar's test for paired proportions(8). All analyses were performed using STATA (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Results:

The study included 332 participants of which 166 had complete data with self-reported adherence and pill counts at all study visits. Missing data was not at random given that individual sites did not contribute to 3 week study visits or pill counts as they were not mandatory study procedures with a payment schedule due to a limited study budget. The mean (SD) age was 64.2 (10.7) years and 36.1% were women. The baseline serum potassium (SD) was 4.8 (0.6) mmol/L. 145 of 166 participants (87.3%) completed the run-in period and were randomized. Of the 21 run-in failures, 10 experienced hyperkalemia, 11 failed to adhere, 2 experienced adverse events that led to drug discontinuation (i.e. gynecomastia), and 1 was unwilling to continue participation (multiple reasons could apply). There were no deaths during the run-in period. Supplementary Table 1 presents baseline characteristics of the 145 randomized participants. Table 1 shows the number of participants with 3 week and 7 week adherence assessments by self-report and pill counts and their results across the categories (<50%, 50-

79%, ≥80%). Supplementary Table 2 shows the adherence measurements in all participants including those with missing data. Supplementary Table 3 shows the potassium monitoring during the run-in period.

166 participants had a 3-week adherence assessment at a mean of 21.8 (3.1) days of whom 146 (94.0%) were adherent (≥80%) by self-report. 166 participants had pill counts at 3 weeks and took a mean of 96.5% (16.1%) of the prescribed tablets resulting in 151 (91.0%) being adherent by pill count. The agreement between self-reported adherence and pill count adherence at 3 weeks was 87.4% with a kappa of 0.11 (95% CI 0 to 0.23, p=0.02) (Table 2).

166 participants had a 7-week adherence assessment at a mean (SD) of 57.1 (9.8) days (range 42 to 92 days) of whom 153 (92.2%) were adherent (≥80%) by self-report. 166 participants had pill counts at 7 weeks and took a mean of 93.3% (14.2%) of the prescribed tablets resulting in 153 (92.2%) being adherent by pill count. The agreement between self-reported adherence and pill count adherence at 7 weeks was 92.2% with a kappa of 0.47 (95% CI 0.34 to 0.59, p<0.001) (Table 3).

In the 166 participants with self-reported adherence assessments at both 3 and 7 weeks, 150 (90.4%) of measurements agreed (kappa=0.27, 95% CI 0.16 to 0.38, p<0.001) (Table 4). Five participants classified as non-adherent at 3 weeks became adherent at 7 weeks while eight participants classified as adherent at 3 weeks were non-adherent at 7 weeks (absolute difference in adherence 2% less at 7 weeks, 95% CI 7% less to 3% more, p=0.58 by McNemar's test). The absolute difference in adherence measured by pill counts was similar (1% more at 7 weeks, 95% CI 5% less to 7% more, p=0.82 by McNemar's test). The percentage of pills taken at both time points correlated moderately with a Pearson's correlation coefficient of 0.32 (95% CI 0.18 to 0.45) (Figure 1) and were similar on the

Bland-Altman plot with a mean difference in the percentage of pills taken (SD) of 3.1% (17.7%) with a 95% limit of agreement of -31.7% to +37.9% (Figure 2).

Supplementary Tables 4, 5 and 6 show the results of the agreement of adherence assessment by self-report and pill counts at 3 weeks, 7 weeks and the agreement between self-report at 3 and 7 weeks using <80% and ≥80% categories. Kappa measured with two categories instead of three categories was marginally improved. Supplementary Table 7 shows the results of agreement calculated using phi instead of kappa due to the high proportion of adherence in study. Phi was approximately 0.15 or higher than kappa in all 4 comparisons. The additional sensitivity analysis including the 332 participants without complete data for all adherence measurements did not meaningfully change our results (Supplementary Table 8).

Discussion:

Principal findings:

In this study of 166 participants with adherence measured at 3 and 7 weeks by self-report and pill counts during an active run-in period, overall adherence was similar regardless of when or how it was measured. These results suggest that a longer run-in period may not substantially improve the identification of non-adherent participants. Self-reported adherence and that measured by pill counts generally agreed but were less concordant at 3 weeks as compared to 7 weeks. Results were not changed using different categories of adherence or measures of agreement that account for extremes of distribution.

Previous studies:

Few studies have empirically evaluated the effects of run-in periods and their designs on the assessment of adherence in RCTs. Although the Cholesterol Reduction in Seniors Program (CRISP) trial demonstrated non-adherent participants during its placebo run-in period were more likely to also be non-adherent during study follow-up, the impact of its run-in period on statistical power was minimal due to the low prevalence of non-adherence in the trial(9). A simulation study of a theoretical RCT by Schechtman et al.(10) showed that run-in periods were most likely to be useful if the randomized proportion of participants is low, non-adherence is characterized as the complete absence of taking study medication, and if partial-adherence (i.e. taking only some of the study medication) markedly attenuates treatment effects. Similarly, Brittain et. al's(11) simulation study suggested that run-in periods are most effective when there is a high proportion of non-adherence [i.e. completely non-adherent participants exist in the trial and there are many "poor adherers" (5-30% of the trial population) with a mean (SD) adherence of 50% (25%) instead of "good adherers" with a mean (SD) adherence of 90% (5%)] and a low rate of misclassification of adherence (i.e. the probability that a potential participant with a true adherence greater or less than a specific threshold will fail or pass the run-in period).

These studies underscore the potential importance of identifying non-adherence accurately. It is reasonable to assume that longer run-in periods improve the identification of non-adherence by permitting participants the opportunity to be correctly classified. However, a recent meta-epidemiologic study of run-in periods did not find a relationship between run-in period duration and either completion rate or the proportion of run-in failures(12). Unfortunately, this analysis was limited by few studies, heterogeneity of populations and interventions, and comparisons were only made between studies rather than within studies. Our SWAT provides an example where 7 weeks had limited

improvement in identifying an adherent RCT population over 3 weeks during an active run-in period for non-adherence and tolerability.

The accuracy of self-reported adherence (with or without the use of formal instruments) and that measured by pill counts has been previously reported in RCTs but has not been specifically evaluated during any run-in period(13). The SPIRIT 2013 guidance for clinical trial protocols suggests that adherence strategies be tailored to each trial's design, intervention and population, but that pragmatic strategies may be desirable so that adherence is comparable to real world settings(14). However, this may be misguided advice if one believes that patients are primarily interested in what happens when they take treatment (i.e. the effect size in an fully adherent population)(15). A systematic review of RCTs of oral pharmacotherapy published in 2010 in high impact general medicine and subspecialty, only 51/111 (45.9%) trials reported adherence measurements of which pill counts were the most common(16). The finding that self-reported adherence agrees with that measured by pill counts at 7 weeks during ACHIEVE's run-in is reassuring for its ongoing use and it may be suitable to simplify study visits in settings where pill counts are not possible or mandatory for regulatory purposes.

Strength and weaknesses of the study

A strength of this study is that that it was embedded within an international RCT for the prevention of CV disease in patients receiving dialysis. ACHIEVE's diverse participant population from many centers is likely representative of not only the global dialysis population, but also other chronic disease populations and trials for primary and secondary prevention. However, dialysis patients may be unique with respect to adherence(17-19), which is multifactorial(20) and incorporates the individual, treatment regimen, patient-provider relationship, clinically setting and disease(21). Dialysis patients frequently have many comorbidities and are an increased risk of adverse events, as seen with even with placebos

in many large RCTs. Whether our results are applicable outside of the setting of dialysis and mineralocorticoid receptor antagonists is uncertain. Adherence was defined as more than 80% of prescribed run-in period study medications by self-report instead of other thresholds. These issues may limit the generalizability of our findings as the relationship between run-in period duration and adherence is presumably influenced by many factors including the trial's population, interventions, type of adherence monitoring and the presence of other eligibility criteria for run-in failures. Generalizability may be further limited by the relatively small number of centers used in this SWAT (less than 50 from Canada, Australia, Uruguay, Brazil, India), the use of active rather than placebo during run-in, and the once daily administration of a tablet with a specific safety profile. However, the use of a once daily oral medication in an older population with multiple comorbidities is common in chronic diseases and therefore is likely to be applicable to other RCTs. ACHIEVE's adherence measurements also do not include other forms of direct and indirect methods(22) including electronic monitoring devices(23), drugs levels or any effect indicators(24) but since self-report is the most practical method of identifying non-adherent participants, this study is reflective of most trials as well as clinical practice(25). The use of a kappa statistic to compare agreement is limited by its ability to get moderate values with extreme results (i.e. there is little possible agreement above chance) as is the case in ACHIEVE's adherence measurements where adherence was more than 90% in most assessment techniques. Lastly, this study does not directly compare whether or not a shorter or longer run-in period is better for adherence monitoring, but rather examines the impact of an additional study visit during run-in on adherence in an observational manner. A RCT comparing run-in period duration or the amount of study visits during run-in on pre and post-randomization adherence would address this question.

Meaning of the study

In summary, this SWAT showed that self-reported adherence and adherence measured by pill counts during an active run-in period were similar between study its 3 and 7 week study visits. Longer run-in periods may not be justified for better identifying non-adherent participants to justify their added complexity and costs. Adherence measurements by self-report were similar those measured by pill counts at 7 weeks, so the latter may not be necessary given their added burden. Additional research regarding the optimal design of run-in periods is needed to inform investigators how to accurately identify non-adherent participants.

Author contributions:

David Collister: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing-Original draft preparation, Visualization **Lawrence Mbuagbaw:** Methodology, Writing-Reviewing and Editing **Gordon Guyatt:** Methodology, Writing- Reviewing and Editing **PJ Devereaux:** Methodology, Writing- Reviewing and Editing **Karthik K. Tennankore:** Writing-Reviewing and Editing **Gilmar Reis:** Writing- Reviewing and Editing **Laura Sola:** Writing-Reviewing and Editing **Denis Xavier:** Writing- Reviewing and Editing **Vivekanand Jha:** Writing-Reviewing and Editing **Martin Gallagher:** Writing- Reviewing and Editing **Antonio L. Dans:** Writing- Reviewing and Editing **Wen Liu:** Writing- Reviewing and Editing **Janak de Zoysa:** Writing-Reviewing and Editing **Camilo Félix:** Writing- Reviewing and Editing **Patrick B Mark:** Writing-Reviewing and Editing **Zuo Li:** Writing- Reviewing and Editing **Jessica Tyrwhitt:** Writing-Reviewing and Editing **Joanne Wilkinson:** Writing- Reviewing and Editing **Patrick Sheridan:** Writing- Reviewing and Editing **Fei Yuan:** Writing- Reviewing and Editing **Michael Walsh:** Conceptualization, Methodology, Writing- Reviewing and Editing, Supervision

Acknowledgements: none

Funding acknowledgements: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declarations of interest: The author(s) declare(s) that there is no conflict of interest.

Research data: The research data is available upon request by with approval from the corresponding author.

Table 1: Adherence measurements during 3 and 7 week run-in period study visits

Study visit	3 weeks	7 weeks
Number of participants	166	166
Study visit timing mean (SD) minimum to maximum	 21.8 (3.1) days 14-35 days	 57.1 (9.8) days 42-92 days
Self-reported adherence: n (%) ≥80% 50-79% <50%	 146 (94.0%) 4 (2.4%) 6 (3.6%)	 153 (92.2%) 11 (6.6%) 2 (1.2%)
Percentage of pills used, mean (SD)	96.5% (16.1%)	93.3% (14.2%)
Adherence measured by pill counts: n (%) ≥80% 50-79% <50%	 151 (91.0%) 12 (7.2%) 3 (1.8%)	 153 (92.2%) 8 (4.8%) 5 (3.0%)

Table 2: Agreement of adherence measured by self-report and pill counts at 3-week run-in period study visit

		Week 3 pill count adherence			
		≥80%	50-79%	<50%	Total
Week 3 self-reported adherence	≥80%	**144**	12	0	156
	50-79%	2	**0**	2	4
	<50%	5	0	**1**	6
	Total	151	12	3	166

Note: agreement = 87.4%, kappa = 0.11 (95% CI 0 to 0.23), p=0.02

Table 3: Agreement of adherence measured by self-report and pill counts at 7-week run-in period study visit

		Week 7 pill count adherence			
		≥80%	50-79%	<50%	Total
Week 7 self-reported adherence	≥80%	**148**	5	0	153
	50-79%	5	**3**	3	11
	<50%	0	0	**2**	2
	Total	153	8	5	166

Note: Agreement = 92.2%, kappa = 0.47 (95% CI 0.34 to 0.59), p<0.001

Table 4: Self-reported agreement of adherence at 3 and 7 week run-in period study visits

		Week 7			
		≥80%	50-79%	<50%	Total
Week 3	≥80%	**148**	7	1	156
	50-79%	3	**1**	0	4
	<50%	2	3	**1**	6
	Total	153	11	2	166

Note: agreement = 90.4%, kappa = 0.27 (95% C.I. 0.16 to 0.38), p<0.001

References:

1. Pablos-Mendez A, Barr RG, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. Jama. 1998;279(3):222-5.
2. Laursen DRT, Paludan-Muller AS, Hrobjartsson A. Randomized clinical trials with run-in periods: frequency, characteristics and reporting. Clin Epidemiol. 2019;11:169-84.
3. Lang JM, Buring JE, Rosner B, Cook N, Hennekens CH. Estimating the effect of the run-in on the power of the Physicians' Health Study. Statistics in medicine. 1991;10(10):1585-93.
4. Lang JM. The use of a run-in to enhance compliance. Statistics in medicine. 1990;9(1-2):87-93; discussion -5.
5. Robiner WN. Enhancing adherence in clinical research. Contemp Clin Trials. 2005;26(1):59-77.
6. Treweek S, Bevan S, Bower P, Campbell M, Christie J, Clarke M, et al. Trial Forge Guidance 1: what is a Study Within A Trial (SWAT)? Trials. 19. England2018. p. 139.
7. Walsh M. Aldosterone bloCkade for Health Improvement EValuation in End-stage Renal Disease (ACHIEVE) 2017 [Available from: https://clinicaltrials.gov/ct2/show/NCT03020303.
8. Mc NQ. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika. 1947;12(2):153-7.
9. Davis CE, Applegate WB, Gordon DJ, Curtis RC, McCormick M. An empirical evaluation of the placebo run-in. Controlled clinical trials. 1995;16(1):41-50.
10. Schechtman KB, Gordon ME. A comprehensive algorithm for determining whether a run-in strategy will be a cost-effective design modification in a randomized clinical trial. Statistics in medicine. 1993;12(2):111-28.
11. Brittain E, Wittes J. The run-in period in clinical trials. The effect of misclassification on efficiency. Controlled clinical trials. 1990;11(5):327-38.
12. Collister D, Rodrigues J, Mbuagbaw L, Devereaux P, Guyatt G, Walsh M. Pre-randomization run-in periods in randomized controlled trials of chronic diseases: a meta-epidemiologic study. (submitted). 2020.
13. Nguyen TM, La Caze A, Cottrell N. What are validated self-report adherence scales really measuring?: a systematic review. Br J Clin Pharmacol. 2014;77(3):427-45.
14. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of Internal Medicine. 2013;158(3):200-7.
15. Walter SD, Guyatt G, Montori VM, Cook R, Prasad K. A new preference-based analysis for randomized trials can estimate treatment acceptability and effect in compliant patients. J Clin Epidemiol. 2006;59(7):685-96.
16. Zhang Z, Peluso MJ, Gross CP, Viscoli CM, Kernan WN. Adherence reporting in randomized controlled trials. Clinical trials (London, England). 2014;11(2):195-204.
17. Ghimire S, Castelino RL, Lioufas NM, Peterson GM, Zaidi ST. Nonadherence to Medication Therapy in Haemodialysis Patients: A Systematic Review. PloS one. 2015;10(12):e0144119.
18. Murali KM, Mullan J, Chen JH, Roodenrys S, Lonergan M. Medication adherence in randomized controlled trials evaluating cardiovascular or mortality outcomes in dialysis patients: A systematic review. BMC nephrology. 2017;18(1):42-017-0449-1.
19. Griva K, Lai AY, Lim HA, Yu Z, Foo MW, Newman SP. Non-adherence in patients on peritoneal dialysis: a systematic review. PloS one. 2014;9(2):e89001.
20. Campbell RJ, Jr. Adherence to medication. The New England journal of medicine. 2005;353(18):1972-4; author reply -4.

21. Ickovics JR, Meisler AW. Adherence in AIDS clinical trials: a framework for clinical research and clinical care. Journal of clinical epidemiology. 1997;50(4):385-91.
22. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther. 1999;21(6):1074-90; discussion 3.
23. Checchi KD, Huybrechts KF, Avorn J, Kesselheim AS. Electronic medication packaging devices and medication adherence: a systematic review. Jama. 2014;312(12):1237-47.
24. Voils CI, Hoyle RH, Thorpe CT, Maciejewski ML, Yancy WS, Jr. Improving the measurement of self-reported medication nonadherence. Journal of clinical epidemiology. 2011;64(3):250-4.
25. Kini V, Ho PM. Interventions to Improve Medication Adherence: A Review. Jama. 320. United States2018. p. 2461-73.