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On behalf of the ACHIEVE investigators*

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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 (25th to 75th 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 \([(100 - \text{the number of pills left in the study bottle})/\text{the number of days at the study visit since entering the run-in period}] \times 100\%\). 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 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:

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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

<table>
<thead>
<tr>
<th>Study visit</th>
<th>3 weeks</th>
<th>7 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>166</td>
<td>166</td>
</tr>
<tr>
<td>Study visit timing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>21.8 (3.1) days</td>
<td>57.1 (9.8) days</td>
</tr>
<tr>
<td>minimum to maximum</td>
<td>14-35 days</td>
<td>42-92 days</td>
</tr>
<tr>
<td>Self-reported adherence: n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80%</td>
<td>146 (94.0%)</td>
<td>153 (92.2%)</td>
</tr>
<tr>
<td>50-79%</td>
<td>4 (2.4%)</td>
<td>11 (6.6%)</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>6 (3.6%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Percentage of pills used, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96.5% (16.1%)</td>
<td>93.3% (14.2%)</td>
</tr>
<tr>
<td>Adherence measured by pill counts: n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80%</td>
<td>151 (91.0%)</td>
<td>153 (92.2%)</td>
</tr>
<tr>
<td>50-79%</td>
<td>12 (7.2%)</td>
<td>8 (4.8%)</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>3 (1.8%)</td>
<td>5 (3.0%)</td>
</tr>
</tbody>
</table>
Table 2: Agreement of adherence measured by self-report and pill counts at 3-week run-in period study visit

<table>
<thead>
<tr>
<th>Week 3 self-reported adherence</th>
<th>Week 3 pill count adherence</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥80%</td>
<td>50-79%</td>
</tr>
<tr>
<td>≥80%</td>
<td>144</td>
<td>12</td>
</tr>
<tr>
<td>50-79%</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>151</td>
<td>12</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Week 7 self-reported adherence</th>
<th>Week 7 pill count adherence</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥80%</td>
<td>148</td>
<td>5</td>
<td>0</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>50-79%</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>153</td>
<td>8</td>
<td>5</td>
<td>166</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Week 3</th>
<th>Week 7</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>50-79%</td>
<td>&lt;50%</td>
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<tr>
<td>&gt;80%</td>
<td>148</td>
<td>7</td>
<td>1</td>
<td></td>
<td>156</td>
</tr>
<tr>
<td>50-79%</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
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Note: agreement = 90.4%, kappa = 0.27 (95% C.I. 0.16 to 0.38), p<0.001
References: