

1 TITLE: Adverse Events During a 12-month Multi-Site and Dose-Response Aerobic Exercise

2 Intervention

3

4 AUTHORS: Eric D. Vidoni¹, George Grove², Amanda N. Szabo-Reed¹, Mickeal N. Key¹, Haiqing

5 Huang³, Jeffrey M. Burns¹, Charles H. Hillman^{4,7}, John M. Jakicic¹, Chaeryon Kang^{9,10}, Arthur F.

6 Kramer^{4,5,6}, Edward McAuley^{5,8}, Lu Wan³, Tera Hawes¹, Sydney S. White¹, and Kirk I. Erickson³

7

8 AUTHOR AFFILIATIONS:

9 1. University of Kansas Medical Center, Kansas City, KS, 66160, USA

10 2. School of Medicine, University of Pittsburgh, Pittsburgh, PA, 15213, USA

11 3. AdventHealth Research Institute, Neuroscience, Orlando, FL, 32804, USA

12 4. Department of Psychology, Northeastern University, Boston, MA, 02115, USA

13 5. Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign,
14 IL, 61801, USA

15 6. Center for Cognitive & Brain Health, Northeastern University, Boston, MA. 02115, USA

16 7. Department of Physical Therapy, Movement, & Rehabilitation Sciences, Northeastern University,
17 Boston, MA, 02115, USA

18 8. Department of Health and Kinesiology, University of Illinois at Urbana Champaign, IL, 61801, USA

19 9. Department of Psychiatry, University of Pittsburgh, PA, 15213, USA

20 10. Department of Biostatistics, University of Pittsburgh, PA, 15213, USA

21

22 CORRESPONDING AUTHOR:

23 Eric D. Vidoni

24 University of Kansas ADRC, MS 6002

25 Fairway, KS 66205

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27 ABSTRACT

28 Purpose: This study aimed to assess the incidence of adverse events (AE) in older adults participating
29 in a year-long exercise intervention, investigating potential dose-response relationships between
30 exercise intensity and AE frequency, and identifying demographic factors associated with AE risk.

31

32 Methods: A total of 648 older adults were randomized into one of three exercise groups: low-intensity
33 stretching and toning (S&T), 150 minutes of aerobic exercise per week (150Ex), or 225 minutes of
34 aerobic exercise per week (225Ex). Adverse events were tracked during the intervention, with event
35 rates calculated based on participant adherence and time in the study. Generalized linear models were
36 employed to compare AE incidence across groups. Post hoc comparisons were used to calculate
37 incidence rate ratios (IRRs) for AE between groups, adjusting for multiple comparisons.

38

39 Results: Overall, 306 AE were reported, with 44% related to the intervention. No significant dose-
40 response relationship was observed for all-cause AE between groups. However, intervention-related AE
41 were more frequent in the aerobic exercise groups. Participants in the 150Ex group had a 77% higher
42 rate of intervention-related AE compared to the S&T group, and the 225Ex group had an 88% higher
43 rate. Higher adherence was associated with fewer all-cause AE, and greater comorbid burden was
44 associated with more AE.

45

46 Conclusions: While aerobic exercise increased the risk of intervention-related AE, the overall risk
47 remained low. Higher adherence to the exercise regimen was associated with fewer AE. These findings
48 suggest aerobic exercise is generally safe in older adults, with the benefits outweighing the risks.

49

50

51 KEY WORDS: Adverse events, dose-response, older adults, adherence, aerobic exercise, safety

52

53 INTRODUCTION

54 Exercise is among the most important health behaviors across the lifespan(1). Exercise is beneficial for
55 cardiovascular,(2) pulmonary,(3) musculoskeletal,(4, 5) and endocrine health.(6) However, exercise is
56 also associated with injuries with more than 8 million medically attended sport and recreation injuries
57 occurring in the United States each year.(7) This incidence does not account for the many more non-
58 medically attended injuries that might prevent or modify exercise behaviors and resolve with self-
59 treatment. Indeed, there is little descriptive evidence regarding the adverse, unintended health
60 consequences of exercise beyond these broad estimates, especially amongst older adults.

61

62 Randomized controlled trials (RCT), with rigorous adverse event (AE), or “medical harms”, reporting are
63 an important potential source of information on exercise-related injuries. AE, typically defined as any
64 untoward medical occurrence (8) are a required component of the Consolidated Standards of Reporting
65 Trials (CONSORT) framework. Standardized reporting of physiologic system involvement, severity, and
66 relatedness, along with other trial data such as demographics may allow for a richer description of
67 exercise risks and benefits in a specific population and minimize the incidence of AE in future exercise
68 trials. The rigor of modern safety monitoring allows for examining the frequency of exercise-related
69 injury and the relationship to other functional factors. However, these important trial experiences are
70 frequently condensed in favor of main outcomes and offered with limited context or investigation.

71

72 Recognizing the potential value of analyzing the frequency of adverse health changes, both related to
73 and independent of exercise, we explored the AE incidence in the Investigating Gains in Neurocognition
74 in an Intervention Trial of Exercise (IGNITE) study (NCT02875301). IGNITE was a multi-site exercise
75 RCT in 648 older adults that was designed to examine the effects of aerobic exercise on cognitive and
76 brain outcomes in late adulthood. IGNITE provided a structured and rigorous foundation to explore
77 several important questions about safety and AE frequency amongst older adults participating in a 12-
78 month exercise regimen: (1) Is there a dose-response relationship between exercise and AE? (2) What

79 is the relative frequency of exercise-related AE to non-related AE? (3) Are there demographic profiles
80 that are more likely to experience exercise-related AE? We hypothesized that the frequency of AE and
81 exercise would vary in relation to the dose of exercise prescribed, with greater doses related to a higher
82 frequency of AE. Further we predicted that individuals with greater comorbid and socioeconomic burden
83 would be at a greater risk for experiencing exercise-related AE.

84

85 METHODS

86 IGNITE enrolled 648 older adults without cognitive impairment or major morbidity into a 1-year exercise
87 trial to measure changes in cognition, brain health, and other outcomes under a previously described
88 protocol.(9) The three sites used a common electronic data capture system, REDCap,(10) allowing for
89 standardized capture of study data including AE. Briefly, participants were block randomized accounting
90 for age and sex into a low intensity stretching and toning control group (S&T), 150 minutes (150Ex) or
91 225 minutes (250Ex) of moderate intensity aerobic exercise (40-60% heart rate reserve), in equal ratio.
92 Participants exercised with supervision of a personal trainer or similar certified professional up to 3
93 times per week with two additional unsupervised sessions 2 times per week. Blood collection and
94 testing for cognitive function, physical function, social and medical history, cardiorespiratory fitness
95 (peak oxygen consumption during a graded exercise test, VO_{2peak}), mental health, brain health, and
96 other outcomes were performed at baseline and 52 weeks, with additional cognitive testing and blood
97 collection at 26 weeks. Germane to this analysis, state-level Area Deprivation Index (11) based on
98 participants' residence at consent, and the Cumulative Illness Rating Scale – Geriatric (CIRS-G) (12)
99 were collected during baseline testing. Exercise adherence was measured as percentage of the
100 prescribed duration completed as reported by the participant on weekly exercise logs. Primary and
101 secondary outcomes will be reported in other manuscripts. The study was approved by the Institutional
102 Review Board of Pittsburgh in adherence to the Declaration of Helsinki, with reliance agreements from
103 other sites. All participants provided written, informed consent.

104

105 Study staff were trained to perform AE inquiry at regular “check-in” intervals approximately every two
106 weeks and at every point of person-to-person communication (e.g. unscheduled gym visits and testing
107 sessions). The typical participant would be questioned regarding health changes approximately 33
108 times by study staff. Trainers were also trained to report medical history changes to the study team. Any
109 reported change in the medical condition of the participant was recorded by study staff at each site as
110 an AE on a standard form that included classifying the physiologic system involved, the relatedness to
111 the study (“Not Related” or “Possibly or Probably Related”), and designation as a Serious Adverse
112 Event (SAE) reportable to our Data and Safety Monitoring Board and sponsor. SAE included
113 hospitalization, life threatening conditions, and death.

114

115 As part of IGNITE standard procedure, pre-existing conditions “discovered” through research testing
116 procedures were characterized. These incidental findings included identification of electrocardiographic
117 evidence of heart disease and abnormal neuroimaging, for example. Typically, these incidental findings
118 required additional clinical review, which delayed enrollment and added to study cost and participant
119 burden. Information on the incidence of these pre-existing conditions in the literature is sparse.
120 Projections of these incidental findings are valuable to those prospectively planning trials and are
121 reported here, separately from AE.

122

123 We compared the incidence of adverse events across intervention groups using generalized linear
124 models with a Poisson distribution.⁽¹³⁾ The models included the intervention group as the independent
125 variable and the number of adverse events as the dependent variable, with an offset for the log-
126 transformed observation period (from consent to the end of testing or participation). A random intercept
127 for each participant was included. Time in trial varied by participant due to reasons such as early
128 withdrawal and COVID-19 lockdown intervention extensions. We assessed model fit by checking for
129 overdispersion and zero-inflation and alternatively fitted a negative binomial and/or zero-inflation
130 corrected regression model if indicated. Following that, we conducted likelihood ratio tests between the

131 full model, including the independent variable, and a reduced model with only the intercept and offset to
132 evaluate the significance of the independent variable as a predictor of adverse event incidence rates.
133 For *post hoc* analysis, we computed estimated marginal means for each category of the independent
134 variable, followed by pairwise comparisons with Tukey's adjustment for multiple comparisons to control
135 the family-wise error rate across all pairwise tests. The resulting incident rate ratios (IRR) from the
136 model reflect the incidence of adverse events per year between categories of the independent variable.

137

138 For demographic comparisons, we divided by the sample median for age (\geq vs $<$ 70y), CIRS-G Total
139 Score (≥ 4 vs. less), Area Deprivation Index (ADI, a measure of socioeconomic disadvantage, 4th state-
140 adjusted decile and above vs. below) and cardiorespiratory fitness (VO_2 peak \geq 20ml/kg/min vs. below),
141 Body Mass Index (BMI) greater than 30 (a clinically relevant cutoff), and sex (female vs. male).
142 Descriptive tables include total AE counts, average counts per person, and average counts per person-
143 year, aiming to provide insights into AE frequency for future studies. All statistical analyses were
144 conducted in R (ver. 4.4.0) using the 'base', 'emmeans', 'glmmTMB', and 'MASS' packages.

145

146 RESULTS

147 Adverse Events Overview: The study team recorded 144 incidental findings and 20 adverse events
148 (AE) during pre-intervention and post-intervention assessment sessions and 306 AE during the
149 intervention, from the 648 individuals randomized into the IGNITE study. Demographics and AE totals
150 are detailed in Table 1.

151

152 Incidental Findings and Adverse Events Outside the Intervention Period: About 1/5th of our participants
153 (n = 134) who were randomized were flagged for an incidental finding that required further evaluation.
154 In total, the 144 incidental findings from these participants were mostly cardiovascular (n = 82) or
155 neurological (n = 53), with 9 other miscellaneous findings. The findings predominantly included
156 electrocardiogram abnormalities evident during exercise testing and MRI abnormalities noted during a

157 mandatory radiology read. Participants also experienced 20 AE during the testing periods. These were
158 coincidental in timing and unrelated to study activities and consisted mostly of upper respiratory
159 infections and musculoskeletal injuries sustained in activities of daily living. Three SAE due to
160 hospitalizations were reported prior to randomization. None of the SAE were related to testing
161 procedures.

162

163 Intervention and Adverse Event Patterns: Because our primary intent for this manuscript was to
164 characterize incidence of AE associated with an exercise intervention, the remaining analyses focus on
165 post-randomization AE. In total, 219 participants reported 306 all-cause AE during their intervention
166 participation (those defined as either related or unrelated to the intervention); 134 were adjudicated to
167 be related to the intervention, and 172 were not related to the intervention. Our primary hypothesis that
168 AE frequency would increase with greater prescribed exercise doses was not supported, as there was
169 no significant dose-response observed for all-cause AE ($\chi^2(2) = 0.23$, $p = 0.89$). Participants
170 experienced 0.47 (SD 0.79) AE on average during their time in the study. Counts for all-cause AE can
171 be found in Table 2.

172

173 When specifically looking at AE judged to be intervention-related, we found that incidence rate ratios
174 (IRR) differed between intervention groups ($\chi^2(2) = 7.05$, $p = 0.03$), but not in a dose-dependent
175 manner. Participants in the 150Ex group trended toward a 77% higher incidence of AE compared to the
176 S&T group (IRR = 1.77, 95% CI [0.96, 3.25], $p = 0.07$). Participants in the 225Ex group had an 88%
177 higher incidence of AE compared to the S&T group (IRR = 1.88, 95% CI [1.03, 3.43], $p = 0.038$). There
178 was no significant difference in the incidence of AE between the 150Ex and 225Ex groups (IRR = 1.05,
179 95% CI [0.63, 1.78], $p = 0.96$). Participants experienced 0.21 (SD 0.66) injuries or other health changes
180 related to exercise per year. Counts for intervention-related AE can be found in Table 3.

181

182 We also assessed AE frequency in the musculoskeletal and cardiovascular systems since these are
183 colloquially associated with exercise injury. There was no significant effect of intervention group on all-
184 cause musculoskeletal AE ($\chi^2(2) = 2.81, p = 0.25$). But much like overall AE, intervention group was a
185 significant factor in musculoskeletal AE related to the intervention ($\chi^2(2) = 8.40, p = 0.02$). Participants
186 in the 150Ex group had a 105% higher incidence of intervention-related musculoskeletal AE compared
187 to the S&T group (IRR = 2.05, 95% CI [1.07, 3.95], $p = 0.03$). Similarly, participants in the 225Ex group
188 had a 103% higher incidence of intervention-related musculoskeletal AE compared to the S&T group
189 (IRR = 2.03, 95% CI [1.05, 3.91], $p = 0.03$). There was no significant difference in the incidence of
190 musculoskeletal AE between the 150Ex and 225Ex groups (IRR = 0.98, 95% CI [0.57, 1.70], $p = 0.99$).
191 There was no difference in related or all-cause cardiac AE between groups ($p > 0.22$). There was also
192 no group difference in the incidence rate of non-intervention related AE ($\chi^2(2) = 1.96, p = 0.37$).

193

194 Finally, we assessed whether exercise prescription adherence was related to AE frequency after
195 accounting for time on intervention. Adherence was significantly associated with fewer all-cause AE
196 (IRR = 0.53, 95% CI: [0.29,0.97], $p = 0.048$). Participants who were fully adherent experienced
197 approximately 47% fewer adverse events. And when considering only intervention-related AE,
198 adherence was not significantly related to AE frequency (IRR = 0.78, 95% CI [0.27, 2.23], $p = 0.653$).

199

200 Adverse Events by Demographics: Contrary to our secondary hypotheses, age, sex, socioeconomic
201 disadvantage, BMI, and baseline cardiorespiratory fitness were unrelated to AE incidence during
202 intervention ($p \geq 0.08$). However, participants with higher comorbidity (CIRS-G Total score at or above
203 the median) had a 40% higher incidence rate of AE compared to those with lower comorbidity burden
204 ($\chi^2(1) = 6.00, p = 0.014, IRR = 1.40, 95\% CI [1.07, 1.83], p = 0.01$), and this was especially true of
205 intervention-related AE. Participants with higher comorbidity had a 70% higher incidence rate of AE
206 compared to those with lower comorbidity (IRR = 1.70, 95% CI [1.16, 2.50], $p < 0.01$).

207

208 Serious Adverse Events and Mortality: During the intervention, 24 participants experienced 27 SAE.
209 Group differences were noted in incidence ($\chi^2(2) = 8.62, p = 0.013$). This was driven exclusively by
210 participants in the 150Ex group having 82.1% lower incidence of SAE compared to those in the S&T
211 group (IRR = 0.18, 95% CI [0.04, 0.84], $p = 0.03$). Three SAE were related to the intervention, one in
212 each intervention group. The related SAE were sudden cardiac death (225 Min), chest pain and
213 hospitalization during exercise (S&T), severe spinal stenosis and hospitalization (150 Min). Additionally,
214 one individual (S&T) was in a motor vehicle accident resulting in death.

215

216 DISCUSSION

217 Our analysis of AE history in the IGNITE trial represents a novel and important, in-depth look at
218 exercise safety in a large multi-site RCT among relatively healthy older adults. We sought to describe
219 the relative frequency of AE in the context of medical and social history profiles linked to AE in older
220 adults who exercise in a manner consistent with public health recommendations. A key question was
221 whether those mode or duration of exercise impacted AE frequency.

222

223 IGNITE offers an opportunity to benchmark AE incidence for partially supervised older adults in
224 exercise programs. Our data suggests that clinical trial staff should expect about 1 medical or health
225 event every 2 years. If engaged in an exercise program targeting a minutes per week and intensity
226 range within public health recommendations, the average adult (65-80 yrs) will experience 0.2 medical
227 or health events related to that exercise program per year, or about 1 injury per 5 exercise years. This
228 low frequency of injury in active older adults should be interpreted as encouraging. Our AE rates are
229 similar to previous reports that about 25% of adults generally engaged in general physical activity will
230 experience an exercise-related injury each year.(14)

231

232 Our primary hypothesis of a dose-response relationship between exercise and AE frequency was not
233 supported by the data. There was no difference in the number of total AE per year between the S&T,

234 150Ex, and 225Ex intervention groups. However, we did find that the aerobic exercise groups
235 experienced more AE deemed “intervention-related”. Our observation of a similar rate of total AE and
236 non-dose-dependence of intervention-related AE across aerobic exercise groups raises several
237 potential interpretations. It is possible that raters experience perception or expectation bias when
238 considering a person in an “active” aerobic exercise group versus the group considered to be a placebo
239 control (S&T). Alternatively, participants in the aerobic exercise groups may be inclined to report AE
240 more frequently. A third possibility is that aerobic exercise conveys some protective benefit against
241 incidental AE unrelated to exercise, such as respiratory infections, which were non-significantly more
242 frequent in the S&T group (see Table 2).

243

244 Consistent with conventional logic, we found that AE frequency was inversely related with adherence to
245 the prescribed amount of exercise over the study, even after accounting for time on intervention. That
246 is, people who were sick or injured less, performed more of their full exercise prescription. Of particular
247 interest, however, was that this relationship only held for all-cause AE. Intervention-related AE were not
248 related to adherence. Possible explanations for this include that the greater doses of exercise was not
249 sufficient to convey greater exercise-related risk. As seen in Table 1, the 225Ex group was not quite as
250 adherence as the other groups. Alternatively, it is possible that the lack of relationship between
251 intervention-related AE and adherence in these 3 groups, is driven largely by the low-risk nature of the
252 stretching and toning intervention and moderate intensity exercise, both of which are considered safe
253 for almost all individuals with age-appropriate cardiovascular and musculoskeletal function.

254

255 In general, we did not find evidence that people with certain demographic characteristics were more
256 likely to report an AE. This included those with a higher BMI, lower cardiorespiratory fitness, age, sex,
257 and those who lived in more resource deprived areas. This is inconsistent with the general
258 understanding of the health risks of being overweight, negative social determinants of health, and poor
259 physical function.(15-18), and could be attributed to a bias of inclusion that is common in many clinical

260 trials.(19, 20) IGNITE did employ a comprehensive list of inclusion and exclusion criteria designed
261 primarily to exclude cognitive impairment from any source. Thus, it is possible that only individuals
262 more resilient to negative health and environmental challenges were selected. However, we found that
263 AE were significantly more frequent in those with greater comorbid burden, which is more in line with
264 common understanding of health risks. Though unreported in our results, we did not identify an
265 interaction of comorbidity and intervention group to suggest that greater intervention duration is of
266 concern for those with greater comorbidity ($p = 0.18$). Future research should examine whether specific
267 comorbid conditions drive exercise-related AE more than others.

268

269 Despite significant rigor, importance, and novelty, there are limitations to this analysis. The IGNITE
270 cohort represents a cognitively unimpaired sample of older adults and a likely-more health resilient
271 population. Analyses such as ours conducted on populations with significant acute or chronic conditions
272 would add to our understanding of exercise safety in the broader population. Additionally, participants
273 received exercise clearance from a licensed provider and underwent baseline testing that identified
274 potential cardiopulmonary risks. This likely biased the sample towards better health. Despite these
275 limitations, our analysis has important implications for lifestyle clinical trials and our understanding of
276 exercise safety for public health recommendations. Our estimates do not inform population-wide
277 estimates of safety but do extend our understanding of the relative frequency of AE and injury. These
278 results are beneficial for the community engaging or seeking to engage in exercise, public health
279 professionals advocating and prescribing exercise, and research teams and regulatory bodies wishing
280 to understand risks associated with exercise. We strongly endorse the rigorous and systematic
281 monitoring of AE in clinical research and the adoption of standardized AE reporting.

282

283 In conclusion, we found exercise to be a safe intervention in a cognitively unimpaired sample of older
284 adults cleared for community exercise by a clinician. Higher comorbidity may convey a greater risk of
285 experiencing an adverse event. But the amount and type of commonly prescribed exercise doses does

286 not appear to convey markedly greater risk for adverse medical events. And the well-documented
287 positive benefits of aerobic exercise far outweigh the modifiable risks.

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294 of Kansas (Infrastructure Grant numbers: P30 AG072973, UL1TR002366; Training Grant T32
295 AG078114).

296

297 Table 1: Demographics of IGNITE Sample

	Intervention Group			
	Overall N = 648	S&T N = 210	150Ex N = 217	225Ex N = 221
Age, yrs	69.8 (3.7)	69.9 (3.7)	69.7 (3.8)	69.8 (3.8)
Female, n	461 / 648 (71.1%)	150 / 210 (71.4%)	154 / 217 (71.0%)	157 / 221 (71.0%)
Education	16.3 (2.2)	16.3 (2.2)	16.4 (2.3)	16.2 (2.2)
CIRS-G Total Score	3.3 (2.4)	3.2 (2.5)	3.4 (2.4)	3.3 (2.4)
Cardiorespiratory fitness, ml/kg/min	21.7 (5.1)	21.5 (5.1)	21.7 (4.8)	21.8 (5.3)
Area Deprivation Index, decile	3.6 (2.7)	3.6 (2.7)	3.6 (2.7)	3.6 (2.8)
Intervention Adherence, % prescribed	78 (38)	80 (37)	82 (37)	74 (39)
Average AE Count Per Person	0.47 (0.79)	0.45 (0.81)	0.47 (0.76)	0.49 (0.81)
Average Intervention-Related AE Count Per Person	0.21 (0.50)	0.13 (0.38)	0.24 (0.56)	0.25 (0.54)
Average AE Count Per Person-Year	0.54 (1.54)	0.53 (1.94)	0.52 (1.16)	0.56 (1.44)
Average Intervention Related AE Count Per Person-Year	0.21 (0.66)	0.16 (0.72)	0.24 (0.72)	0.23 (0.52)
¹ Mean (SD); n / N (%)				

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Table 2: All-cause AE by System During the Intervention Period

	Intervention Group		
	S&T	150Ex	225Ex
All	95 0.45 0.03	103 0.47 0.03	108 0.49 0.03
Musculoskeletal	45 0.21 0.19	62 0.29 0.24	68 0.31 0.27
Cardiovascular	11 0.05 0.05	9 0.04 0.04	8 0.04 0.03
Integument	5 0.02 0.02	6 0.03 0.02	6 0.03 0.02
Neurological	5 0.02 0.02	2 0.01 0.01	2 0.01 0.01
Optic	1 0.00 0.00	2 0.01 0.01	1 0.00 0.00
Vestibular	1 0.00 0.00	0 0.00 0.00	0 0.00 0.00
Oral	0 0.00 0.00	3 0.01 0.01	2 0.01 0.01
Psychiatric	0 0.00 0.00	0 0.00 0.00	1 0.00 0.00
Gastrointestinal	2 0.01 0.01	2 0.01 0.01	7 0.03 0.03
Genitourinary	2 0.01 0.01	3 0.01 0.01	3 0.01 0.01
Endocrine	2 0.01 0.01	0 0.00 0.00	0 0.00 0.00
Respiratory	9 0.04 0.04	9 0.04 0.04	8 0.04 0.03
Immune	0 0.00 0.00	1 0.00 0.00	0 0.00 0.00
Gynecologic	1 0.00 0.00	1 0.00 0.00	1 0.00 0.00
Other	11 0.05 0.05	3 0.01 0.01	1 0.00 0.00

Values are n | average # of events per person | average # of events per person-year

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Table 3: Intervention-Related AE by System During the Intervention Period

	Intervention Group					
	S&T		150Ex		225Ex	
All	28	0.13 0.01	51	0.24 0.01	55	0.25 0.01
Musculoskeletal	22	0.10 0.09	47	0.22 0.18	47	0.21 0.18
Cardiovascular	6	0.03 0.02	4	0.02 0.02	1	0.00 0.00
Integument	0	0.00 0.00	0	0.00 0.00	2	0.01 0.01
Neurological	0	0.00 0.00	0	0.00 0.00	1	0.00 0.00
Optic	0	0.00 0.00	0	0.00 0.00	0	0.00 0.00
Vestibular	0	0.00 0.00	0	0.00 0.00	0	0.00 0.00
Oral	0	0.00 0.00	0	0.00 0.00	0	0.00 0.00
Psychiatric	0	0.00 0.00	0	0.00 0.00	0	0.00 0.00
Gastrointestinal	0	0.00 0.00	0	0.00 0.00	1	0.00 0.00
Genitourinary	0	0.00 0.00	0	0.00 0.00	1	0.00 0.00
Endocrine	0	0.00 0.00	0	0.00 0.00	0	0.00 0.00
Respiratory	0	0.00 0.00	0	0.00 0.00	1	0.00 0.00
Immune	0	0.00 0.00	0	0.00 0.00	0	0.00 0.00
Gynecologic	0	0.00 0.00	0	0.00 0.00	0	0.00 0.00
Other	0	0.00 0.00	0	0.00 0.00	1	0.00 0.00

Values are n | average # of events per person | average # of events per person-year

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