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Delivering clinical studies of exercise in the COVID-19 pandemic: Challenges and adaptations using a feasibility trial of isometric exercise to treat hypertension as an exemplar.

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3 1 **Delivering clinical studies of exercise in the COVID-19 pandemic: Challenges and**
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5 2 **adaptations using a feasibility trial of isometric exercise to treat hypertension as an**
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7 3 **exemplar.**
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ABSTRACT

The COVID-19 pandemic has significantly impacted upon the delivery of clinical trials in the UK, posing complicated organisational challenges and requiring adaptations; especially to exercise intervention studies based in the community. We aim to identify the challenges of public involvement, recruitment, consent, follow-up, intervention and the healthcare professional (HCP) delivery aspects of a feasibility study of exercise in hypertensive primary care patients during the COVID-19 pandemic. Whilst these challenges elicited many reactive changes which were specific to, and only relevant in the context of 'lockdown' requirements, some of the protocol developments that came about during this unprecedented period have great potential to inform more permanent practices for carrying out this type of research. To this end, we detail the necessary adaptations to many elements of the feasibility study and critically reflect upon our approach to redesigning and amending this ongoing project in order to maintain its viability to date. Some of the more major protocol adaptations, such as moving the study to remote means wherever possible, had further unforeseen and undesirable outcomes (e.g. additional appointments) with regards to extra resources required to deliver the study. However, other changes improved the efficiency of the study, such as the remote informed consent and the direct advertising with pre-screening survey. The adaptations to the study have clear links to the UK Plan for the future of research delivery. It is intended that this specific documentation and critical evaluation will help those planning or delivering similar studies to do so in a more resource efficient and effective way. In conclusion, it is essential to reflect and respond with protocol changes in the current climate in order to deliver clinical research successfully.

47 INTRODUCTION

48 The recent outbreak of coronavirus disease-2019 (COVID-19)[1] and the international response
49 to impose “stay at home” orders resulted in most clinical trials being suspended to recruitment,
50 with the exception of those directly related to the pandemic. In May 2020, the National Institute
51 for Health and Care Research (NIHR) issued guidance for restarting research paused due to
52 COVID-19 for the UK[2] based upon key guiding principles: viability (scientific, clinical,
53 financial or practical reasons), safety, capacity and prioritisation. Whilst these are fundamental to
54 appropriate conduct of clinical trials, it is evident that changes during and following the
55 pandemic present significant organisational challenges.

56
57 To help plan and undertake clinical research in the current climate, a structured approach to the
58 redesign of clinical trials is described by Karzai *et al.*[3] who draw attention to eligibility criteria,
59 correlative studies, telehealth and partnerships, with particular emphasis on logistics of clinical
60 trials and suggest that embracing change is vital.

61
62 The Medidata group recently identified that data completeness and collection have been a key
63 problem in the pandemic[4] and to mitigate some of the new challenges facing researchers, many
64 regulatory authorities acknowledged the need to allow adaptations to trial recruitment, consent
65 and monitoring[5].

66
67 Here, we critically reflect upon our approach to redesigning/amending a feasibility study of the
68 impact of isometric exercise (IE) on arterial hypertension in otherwise healthy adults. This trial
69 involved identification of people with stage 1 hypertension[6], not on anti-hypertensive

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3 70 medication and with no relevant co-morbidity. Participants were randomised to a period of
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5 71 isometric/static exercise (IE) and standard care ‘lifestyle’ advice (SCA) or control (SCA alone).
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8 72 End points included deliverability in the NHS (particularly primary care), fidelity of the
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10 73 intervention and impact on blood pressure (BP)[7].
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14 75 We estimate that workload to deliver this project increased by >50% with the advent of COVID-
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16 76 19, e.g. the Study Steering Committee needed to meet 3-monthly versus 6-monthly. The physical
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18 77 exercise nature of the trial also brought specific challenges for governance, safety and conduct,
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20 78 including evaluation of participant eligibility and informed consent along with the prescription of
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22 79 IE originally designed to be face-to-face. The study includes physiological measures of fidelity,
23
24 80 e.g. BP and heart rate (HR) responses to exercise, and remote monitoring systems needed to be
25
26 81 developed for reliable collection of these data. By nature, exercise interventions require ongoing
27
28 82 participant motivation[8] and additional methods to support this remotely were required. Because
29
30 83 of the reduction in routine and face-to-face follow-up appointments, as well as changes to coding
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32 84 strategy in primary care, fewer patients were identified following searches of GP systems than in
33
34 85 pilot work. Indeed, Dale *et al.* suggested that nearly 500,000 fewer people were identified and
35
36 86 treated for hypertension in mainland UK from March 2020-2021 compared to the previous
37
38 87 year[9]. Paradoxically, it has been reported that the pandemic has heightened the need to focus
39
40 88 on lowering the incidence of cardiovascular disease risk factors such as high BP[10]. Whilst
41
42 89 physical activity has been identified as a primary focus for cardiovascular disease
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44 90 prevention[11], it is likely that pre-existing barriers to exercise prescription and promotion (e.g.
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46 91 GP perceived status of exercise), have been exacerbated by the pandemic[12]. Recent research
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48 92 suggests that existing reticence amongst GPs based on lack of tradition, as well as lack of
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3 93 knowledge and validated tools[13] is likely to have reduced the probability of exercise
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5 94 interventions being implemented. It was therefore necessary to reassess the capacity for NHS
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8 95 primary care staff to deliver the study and ultimately required a fundamental change to
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10 96 recruitment strategies. To help mitigate the impact COVID-19 has caused to research in the
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12 97 NHS, the Department for Health and Social Care (DHSC) launched their strategy regarding the
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14 98 future of UK research delivery[14], recognizing five key themes, three of which are directly
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16 99 addressed in the commentary section of this paper: (2) patient centered, (3) streamlined, efficient
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18 100 and innovative and (4) research enabled by data and digital tools.
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24 102 We aim to identify the challenges of patient and public involvement, recruitment, consent,
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26 103 follow-up, intervention aspects and primary care staff delivery of a feasibility study of exercise
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28 104 during the COVID-19 pandemic.
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34 106 **COMMENTARY**

37 107 **Patient and public involvement and engagement (PPIE)**

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40 108 Study delivery has benefited from lay members of the project management group, which allowed
41
42 109 an integrated approach to redesign. Their previous experience and insight have been invaluable
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44 110 when commenting on important issues, offering a patient perspective to all elements of the
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46 111 redesign including: patient access to technology, use of personal protective equipment,
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48 112 optimising reminder texts (to mitigate attrition) and improving the participant documents and
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50 113 resources. As acknowledged by the NIHR[15], PPIE has been essential in successfully adapting
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52 114 the study for remote delivery during the pandemic and beyond.
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3 115 The considerable time delays caused by COVID-19 restrictions along with the numerous
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5 116 amendments, contributed to the significant increase in workload for the research team; arguably
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8 117 this disproportionately impacts upon lay members whose continued involvement is no longer
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10 118 commensurate with initial commitment expectations. Interestingly, similar difficulties have
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12 119 resulted in many COVID-19 trials sacrificing valuable PPIE to meet time constraint
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14 120 pressures[16]. We have been extremely fortunate with the loyalty and commitment received
15
16 121 from our public members and would advise anyone embarking on a funded research path to
17
18 122 ensure they select these members with care. The importance of careful ongoing consideration of
19
20 123 this aspect is reiterated in the UK-wide vision for the future of clinical research delivery which
21
22 124 identifies the need to strengthen PPIE in research[14].
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27 125 **Changes to trial protocol and governance**

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29 126 As a result of COVID-19 restrictions, alterations had to be made to the study protocol, along
30
31 127 with ethical amendments and this inevitably introduced significant delay to delivery of the
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33 128 study[17]. One major alteration involved moving all contact to remote means wherever possible,
34
35 129 including the screening, baseline and follow-up visits. This clearly aligns with the DHSC's
36
37 130 fourth key theme to ensure research is enabled by data and digital tools [14]. This meant an
38
39 131 additional remote appointment had to be added to screen and check patient eligibility and clinic
40
41 132 BP measurements were replaced by participant home BP readings using Omron M3 Intellisense
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43 133 machines resulting in increased study costs. Also, this raised potential concerns regarding the
44
45 134 accuracy of using this type of BP monitor[18]: despite the device being validated[19] and the use
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47 135 of remotely observed BP measurements by a trained HCP.
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3 137 As a result of social distancing guidelines, participants were asked to carry out home BP readings
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5 138 with the investigator via video call. This was to ensure accurate home BP measurements
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8 139 according to NICE guidelines[6]. The disadvantage of this approach was that participants needed
9
10 140 access to technology which PPIE advised to avoid. Implementing this major change in delivery
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12 141 required additional equipment, such as webcam access, instructional resources (e.g. videos), and
13
14 142 alternative arrangements for those without IT access or ability i.e. free provision of smart
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16 143 technology or an additional visit. Thus, there were further logistical and cost implications
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18 144 associated with continued attempts to avoid inequity of access.
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24 146 Due to reduced face-to-face contact with participants, it was necessary to develop a remote
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26 147 reminder system to mitigate increased risk of drop out. The sending of the messages was
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28 148 completely automated and made use of an SMS API provided by a large provider, with this
29
30 149 system now reusable for future studies.
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35 151 **Adaptation of participant identification searches and recruitment**

36
37 152 The pandemic made recruitment more challenging for several reasons including a reduction of
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39 153 patients identified with stage 1 hypertension on GP records, reduced access to GP administrative
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41 154 staff and less provision of research active staff in primary care.
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47 156 Searches of GP records yielded considerably fewer patients than pilot work had indicated. This is
48
49 157 primarily attributed to: reduced attendances at GP clinics, suspension of routine health checks
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51 158 (e.g., well man over 50), reduced recording of hypertension in primary care (suspension of some
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53 159 indicators in the quality and outcomes framework) and lack of repeat attendance for suspected
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3 160 hypertension. This hypothesis is supported by the findings of Dale *et al.*[10], who demonstrate a
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5 161 considerable reduction in numbers treated for incident hypertension during the pandemic.
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7 162 Anecdotal evidence also suggests that because GPs were concerned about being able to follow
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9 163 patients up (during the pandemic), many were commenced on antihypertensive medication
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11 164 immediately following diagnosis rather than allowing a period of lifestyle modification as per
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13 165 hypertension guidelines[6]. Since our study recruited untreated hypertensives, this rendered them
14
15 166 ineligible. In future, initiatives such as rollout of the NHS community pharmacy BP check
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17 167 service[20] may mean potential participants for hypertension studies are identified outside the
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19 168 GP setting and supports the need for a more data-enabled research environment[14].
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26 170 As a result of persistent difficulties with recruiting in primary care, the study was approved for
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28 171 delivery in all NHS settings with additional direct to patient advertising. This targeted potential
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30 172 participants geographically via Facebook social media within reasonable travel distance of a
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32 173 research site. In addition, those displaying interest in subjects that may predispose them to being
33
34 174 attracted to the study were targeted. Users seeing the advert could click through to a pre-
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36 175 screening survey to find out if they were eligible to take part in the study and register their
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38 176 details[21]. This led to a greater number of potential participants (75% of those randomised)
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40 177 without involving any NHS staff time. This method also elicited a lower percentage of screen
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42 178 failures compared to GP screening and mail out (31% screen failure rate for direct advertising
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44 179 compared to 67% for mail out). Key learning has been the effectiveness of the pre-screening
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46 180 survey in significantly reducing staff time (up to 12-hours of screening patient lists before
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48 181 mailout) and screen failure rates.
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183 **Adaptations to consent**

184 The requirement to reduce face-to-face contact with participants meant that, although consent
185 remained a requirement, this process had to be managed virtually with the HCP on the video call
186 and participants completing and signing an online form. In line with the drive for research to be
187 enabled by digital tools[14], this data is now captured straight into Qualtrics (online system)
188 which is directly accessible by the research team. This allowed more efficient and accurate data
189 handling without the need to transfer data from paper to database. In general, this worked well,
190 however there were some cases where it did not, primarily because patients were unable to
191 access both Microsoft Teams and Qualtrics simultaneously.

193 **Changes to the intervention - prescription and development of isometric exercise training**

194 The IE intervention used is a wall squat (Figure 1) protocol, which involves leaning against a
195 wall and squatting at an individual specific (knee joint) angle prescribed to elicit the required
196 exercise intensity based upon HR [22].

198 Figure 1. Isometric wall squat exercise

200 To accurately prescribe an individual specific wall squat angle, participants must complete at
201 least three-stages of a five-stage incremental isometric exercise test (IIET)[23]. It was originally
202 intended to subjectively pre-assess each patient's physical ability to meet this requirement during
203 the initial face-to-face screening visit. However, since this was replaced with a remote screening
204 visit, it was not possible to complete this capability assessment in person. As such, we had to
205 develop a simple protocol to be completed remotely via video call. This protocol tested the

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3 206 participant's ability to reach an approximation of their personalised IE training angle and hold
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5 207 for 60-seconds. The easy-to-follow instructions allow participants to carry out the test
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7 208 independently. Delivering the test remotely required additional risk assessment, the translation of
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9 209 safety considerations into the home (e.g. a nearby chair for support), along with additional online
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11 210 instructional materials.
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17 212 The IIET stayed the same apart from the time delay of having to establish the status of the
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19 213 exercise type as non-aerosol generating; expert consensus from the Physiological Society was
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21 214 not available until 20th May 2020[24]. However, new personal protective equipment (PPE)
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23 215 considerations had to be implemented immediately in line with government guidelines[25]. This
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25 216 had numerous implications, not least equipment costs and additional time considerations during
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27 217 face-to-face testing.
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33 219 **Impact of COVID-19 on NHS primary care staff participation**

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35 220 It was originally planned to recruit 2-4 primary care sites in the Southeast based upon feasibility
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37 221 searches performed before the pandemic. Between November 2019 and February 2020, one site
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39 222 had committed in principle as a research site. The onset of COVID-19 and unprecedented
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41 223 demands on the NHS, in particular primary care, led to initial difficulties in identifying principal
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43 224 investigators at prospective sites due to uncertainty of workload. Identification of appropriate
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45 225 HCPs with the capacity to deliver the intervention was already a challenge. This was exacerbated
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47 226 by the fact that GP principal investigators were focused on the COVID-19 response and, later,
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49 227 COVID-19 intervention studies and vaccination.
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229 Embedding clinical research in the NHS is a key theme in the vision of *The Future of UK*
230 *Clinical Research Delivery*[14]. To create a research-positive culture in which all health and care
231 staff feel empowered to support and participate in clinical research as part of their job role, much
232 greater funding and resourcing of primary care would be necessary. To try and mitigate this in
233 the current study we were forced to approach sites further afield and would strongly recommend
234 over-planning the number of sites in future exercise-based studies.

236 **Conclusions**

237 Delivery of clinical trials in a safe and reliable way has always been complex, requiring good
238 governance and ethical frameworks, as well as robust infrastructure. Whilst there are many
239 randomised controlled trials of exercise either published or planned, their use is more limited
240 than conventional trials of medicinal products. In addition, there are barriers to the prescription
241 of exercise by HCPs. These issues became more acute during the COVID-19 pandemic where,
242 quite reasonably, trials directed at intervention in COVID-19 were prioritised[3]. However, it is
243 evident that abandoning preventative healthcare measures has had (and more concerningly will
244 continue to have) a deleterious effect on the general population.

246 We have discussed several predictable hurdles the pandemic created for recruitment to a
247 feasibility study of IE. Other unexpected problems have also arisen, such as a significant
248 reduction in the number of people identified with stage 1 hypertension . Ironically, the pandemic
249 presented opportunities such as unprecedented speed and fluidity of change to the study
250 approach. Remote consent and screening of patients, automated reminders, and video validation
251 of BP technique were all developed, approved and tested more rapidly as a result of necessity.

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3 252 However, this impacted directly upon our original commitment to ensure equality of access due
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5 253 to the associated IT requirements and level of IT literacy required to engage remotely e.g., need
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8 254 for webcams, two screens open etc. Overall, a willingness to constantly reflect and respond with
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10 255 protocol changes is essential in the current climate.
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14 257 Since we were unable to identify eligible patients through primary care, we sought and gained
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16 258 approval for direct marketing of the study resulting in a tremendous response (1362 click-
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18 259 throughs from 63 days of active social media advertising), indicating public willingness and
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20 260 enthusiasm for this type of research. Central databases, opt-in to research and direct marketing
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22 261 (where appropriate) are likely to be much more effective methods for future study recruitment.
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26 263 Finally, it may be worth considering a consensus statement from leaders in the field of exercise
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28 264 research to find common ways to enhance recruitment to trials of exercise to augment current
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30 265 clinical practice.
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40 358 **AUTHORS’ CONTRIBUTIONS**

41
42 359 Chris Farmer, Jim Wiles, Melanie Rees-Roberts, Jamie O’Driscoll and Douglas MacInnes
43
44 360 designed the original study concept and design. COVID-19 adaptations were implemented by the
45
46 361 Chris Farmer and Jim Wiles as co-leads during COVID-19 and learnings collated by Ellie Santer
47
48 362 for this paper. The first draft of the manuscript was written by Chris Farmer, Jim Wiles, Ellie
49
50 363 Santer and further developed by Melanie Rees-Robers, Alan West, John Darby. The paper was
51
52 364 then reviewed by Douglas MacInnes, Vanessa Short, Katerina Gousia, Tracy Pellatt-Higgins,
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3 365 Tim Doulton and Jamie O’Driscoll. The study has two lay co-applicants (Alan West and John
4
5 366 Darby) who are involved as members of the research team and make shared decisions on the
6
7 367 study. Alan West and John Darby directly contributed to drafting and reviewing the content of
8
9 368 this manuscript on Patient and Public Involvement during COVID. Pauline Swift is chair of the
10
11 369 Study Steering Committee and with Tim Doulton reviewed drafts of this manuscript for clinical
12
13 370 aspects within national context of hypertension treatment.
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39
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3 1 **Delivering clinical studies of exercise in the COVID-19 pandemic: Challenges and**
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5 2 **adaptations using a feasibility trial of isometric exercise to treat hypertension as an**
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7 3 **exemplar.**
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24 **ABSTRACT**

25 The COVID-19 pandemic has significantly impacted upon the delivery of clinical trials in the
26 UK, posing complicated organisational challenges and requiring adaptations; especially to
27 exercise intervention studies based in the community. We aim to identify the challenges of
28 public involvement, recruitment, consent, follow-up, intervention and the healthcare professional
29 (HCP) delivery aspects of a feasibility study of exercise in hypertensive primary care patients
30 during the COVID-19 pandemic. Whilst these challenges elicited many reactive changes which
31 were specific to, and only relevant in the context of 'lockdown' requirements, some of the
32 protocol developments that came about during this unprecedented period have great potential to
33 inform more permanent practices for carrying out this type of research. To this end, we detail the
34 necessary adaptations to many elements of the feasibility study and critically reflect upon our
35 approach to redesigning and amending this ongoing project in order to maintain its viability to
36 date. Some of the more major protocol adaptations, such as moving the study to remote means
37 wherever possible, had further unforeseen and undesirable outcomes (e.g. additional
38 appointments) with regards to extra resources required to deliver the study. However, other
39 changes improved the efficiency of the study, such as the remote informed consent and the direct
40 advertising with pre-screening survey. The adaptations to the study have clear links to the UK
41 Plan for the future of research delivery. It is intended that this specific documentation and critical
42 evaluation will help those planning or delivering similar studies to do so in a more resource
43 efficient and effective way. In conclusion, it is essential to reflect and respond with protocol
44 changes in the current climate in order to deliver clinical research successfully; as in the case of
45 this particular study.

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3 47 Strengths and limitations of the study
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- 5 48 • The protocol developments documented provide a useful resource to other researchers
6
7 and research managers tasked with delivering physical activity / applied research trials in
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9 a ‘post covid’ environment.
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11 • The structured approach to the redesign of this clinical trial clearly highlights the
12 51
13 advantage of having integrated and comprehensive patient and public involvement
14 52
15 • Recommendations are being made based upon the delivery of a small-scale feasibility
16 53
17 study
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19 • The adaptations and implications identified may not be generalisable to all types of study
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21 design
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29 58 **INTRODUCTION**

30
31 59 The recent outbreak of coronavirus disease-2019 (COVID-19)[1] and the international response
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33 60 to impose “stay at home” orders resulted in most clinical trials being suspended to recruitment,
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35 61 with the exception of those directly related to the pandemic. In May 2020, the National Institute
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37 62 for Health and Care Research (NIHR) issued guidance for restarting research paused due to
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39 63 COVID-19 for the UK[2] based upon key guiding principles: viability (scientific, clinical,
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41 64 financial or practical reasons), safety, capacity and prioritisation. Whilst these are fundamental to
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43 65 appropriate conduct of clinical trials, it is evident that changes during and following the
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45 66 pandemic present significant organisational challenges.
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52 68 To help plan and undertake clinical research in the current climate, a structured approach to the
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54 69 redesign of clinical trials is described by Karzai *et al.*[3] who draw attention to eligibility criteria,
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3 70 correlative studies, telehealth and partnerships, with particular emphasis on logistics of clinical
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5 71 trials and suggest that embracing change is vital.
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10 73 The Medidata group recently identified that data completeness and collection have been a key
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12 74 problem in the pandemic[4] and to mitigate some of the new challenges facing researchers, many
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14 75 regulatory authorities acknowledged the need to allow adaptations to trial recruitment, consent
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16 76 and monitoring[5].
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21 78 Here, we critically reflect upon our approach to redesigning/amending a feasibility study of the
22
23 79 impact of isometric exercise (IE) on arterial hypertension in otherwise healthy adults. This trial
24
25 80 involved identification of people with stage 1 hypertension[6], not on anti-hypertensive
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27 81 medication and with no relevant co-morbidity. Participants were randomised to a period of
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29 82 isometric/static exercise (IE) and standard care 'lifestyle' advice (SCA) or control (SCA alone).
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31 83 End points included deliverability in the NHS (particularly primary care), fidelity of the
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33 84 intervention and impact on blood pressure (BP)[7].
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40 86 We estimate that workload to deliver this project increased by >50% with the advent of COVID-
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42 87 19, e.g. the Study Steering Committee needed to meet 3-monthly versus 6-monthly. The physical
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44 88 exercise nature of the trial also brought specific challenges for governance, safety and conduct,
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46 89 including evaluation of participant eligibility and informed consent along with the prescription of
47
48 90 IE originally designed to be face-to-face. The study includes physiological measures of fidelity,
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50 91 e.g. BP and heart rate (HR) responses to exercise, and remote monitoring systems needed to be
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52 92 developed for reliable collection of these data. By nature, exercise interventions require ongoing
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3 93 participant motivation[8] and additional methods to support this remotely were required. Because
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5 94 of the reduction in routine and face-to-face follow-up appointments, as well as changes to coding
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7 95 strategy in primary care, fewer patients were identified following searches of GP systems than in
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9
10 96 pilot work. Indeed, Dale *et al.* suggested that nearly 500,000 fewer people were identified and
11
12 97 treated for hypertension in mainland UK from March 2020-2021 compared to the previous
13
14 98 year[9]. Paradoxically, it has been reported that the pandemic has heightened the need to focus
15
16 99 on lowering the incidence of cardiovascular disease risk factors such as high BP and obesity
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18
19 100 [10]. Whilst physical activity has been identified as a primary focus for cardiovascular disease
20
21 101 prevention[11], it is likely that pre-existing barriers to exercise prescription and promotion (e.g.
22
23 102 GP perceived status of exercise), have been exacerbated by the pandemic[12]. Recent research
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25 103 suggests that existing reticence amongst GPs based on lack of tradition, as well as lack of
26
27 104 knowledge and validated tools[13] is likely to have reduced the probability of exercise
28
29 105 interventions being implemented. It was therefore necessary to reassess the capacity for NHS
30
31 106 primary care staff to deliver the study and ultimately required a fundamental change to
32
33 107 recruitment strategies. To help mitigate the impact COVID-19 has caused to research in the
34
35 108 NHS, the Department for Health and Social Care (DHSC) launched their strategy regarding the
36
37 109 future of UK research delivery[14], recognizing five key themes, three of which are directly
38
39 110 addressed in the commentary section of this paper: (2) patient centered, (3) streamlined, efficient
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41 111 and innovative and (4) research enabled by data and digital tools.
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49 113 We aim to identify the challenges of patient and public involvement, recruitment, consent,
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51 114 follow-up, intervention aspects and primary care staff delivery of a feasibility study of exercise
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53 115 during the COVID-19 pandemic.
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COMMENTARY**Patient and public involvement and engagement (PPIE)**

Study delivery has benefited from lay members of the project management group, which allowed an integrated approach to redesign. Their previous experience and insight have been invaluable when commenting on important issues, offering a patient perspective to all elements of the redesign including: patient access to technology, use of personal protective equipment, optimising reminder texts (to mitigate attrition) and improving the participant documents and resources. As acknowledged by the NIHR[15], PPIE has been essential in successfully adapting the study for remote delivery during the pandemic and beyond.

The considerable time delays caused by COVID-19 restrictions along with the numerous amendments, contributed to the significant increase in workload for the research team; arguably this disproportionately impacts upon lay members whose continued involvement is no longer commensurate with initial commitment expectations. Interestingly, similar difficulties have resulted in many COVID-19 trials sacrificing valuable PPIE to meet time constraint pressures[16]. We have been extremely fortunate with the loyalty and commitment received from our public members and would advise anyone embarking on a funded research path to ensure they select these members with care. The importance of careful ongoing consideration of this aspect is reiterated in the UK-wide vision for the future of clinical research delivery which identifies the need to strengthen PPIE in research[14].

Changes to trial protocol and governance

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2
3 137 As a result of COVID-19 restrictions, alterations had to be made to the study protocol, along
4
5 138 with ethical amendments and this inevitably introduced significant delay to delivery of the
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8 139 study[17]. One major alteration involved moving all contact to remote means wherever possible,
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10 140 including the screening, baseline and follow-up visits. This clearly aligns with the DHSC's
11
12 141 fourth key theme to ensure research is enabled by data and digital tools [14]. This meant an
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14 142 additional remote appointment had to be added to screen and check patient eligibility and clinic
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16 143 BP measurements were replaced by participant home BP readings using Omron M3 Intellisense
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18 144 machines resulting in increased study costs. Also, this raised potential concerns regarding the
19
20 145 accuracy of using this type of BP monitor[18]: despite the device being validated[19] and the use
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22 146 of remotely observed BP measurements by a trained HCP.
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28 148 As a result of social distancing guidelines, participants were asked to carry out home BP readings
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30 149 with the investigator via video call. This was to ensure accurate home BP measurements
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32 150 according to NICE guidelines[6]. The disadvantage of this approach was that participants needed
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34 151 access to technology which PPIE advised to avoid. Implementing this major change in delivery
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36 152 required additional equipment, such as webcam access, instructional resources (e.g. videos), and
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38 153 alternative arrangements for those without IT access or ability i.e. free provision of smart
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40 154 technology or an additional visit. Thus, there were further logistical and cost implications
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42 155 associated with continued attempts to avoid inequity of access.
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49 157 Due to reduced face-to-face contact with participants, it was necessary to develop a remote
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51 158 reminder system to mitigate increased risk of drop out. The sending of the messages was
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3 159 completely automated and made use of an SMS API provided by a large provider, with this
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5 160 system now reusable for future studies.
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162 **Adaptation of participant identification searches and recruitment**

163 The pandemic made recruitment more challenging for several reasons including a reduction of
164 patients identified with stage 1 hypertension on GP records, reduced access to GP administrative
165 staff and less provision of research active staff in primary care.
166

167 Searches of GP records yielded considerably fewer patients than pilot work had indicated. This is
168 primarily attributed to: reduced attendances at GP clinics, suspension of routine health checks
169 (e.g., well man over 50), reduced recording of hypertension in primary care (suspension of some
170 indicators in the quality and outcomes framework) and lack of repeat attendance for suspected
171 hypertension. This hypothesis is supported by the findings of Dale *et al.*[10], who demonstrate a
172 considerable reduction in numbers treated for incident hypertension during the pandemic.

173 Anecdotal evidence also suggests that because GPs were concerned about being able to follow
174 patients up (during the pandemic), many were commenced on antihypertensive medication
175 immediately following diagnosis rather than allowing a period of lifestyle modification as per
176 hypertension guidelines[6]. Since our study recruited untreated hypertensives, this rendered them
177 ineligible. In future, initiatives such as rollout of the NHS community pharmacy BP check
178 service[20] may mean potential participants for hypertension studies are identified outside the
179 GP setting and supports the need for a more data-enabled research environment[14].
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3 181 As a result of persistent difficulties with recruiting in primary care, the study was approved for
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5 182 delivery in all NHS settings with additional direct to patient advertising. This targeted potential
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8 183 participants geographically via Facebook social media within reasonable travel distance of a
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10 184 research site. In addition, those displaying interest in subjects that may predispose them to being
11
12 185 attracted to the study were targeted. Users seeing the advert could click through to a pre-
13
14 186 screening survey to find out if they were eligible to take part in the study and register their
15
16 187 details[21]. This led to a greater number of potential participants (75% of those randomised)
17
18 188 without involving any NHS staff time. This method also elicited a lower percentage of screen
19
20 189 failures compared to GP screening and mail out (31% screen failure rate for direct advertising
21
22 190 compared to 67% for mail out). Key learning has been the effectiveness of the pre-screening
23
24 191 survey in significantly reducing staff time (up to 12-hours of screening patient lists before
25
26 192 mailout) and screen failure rates.
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32 33 194 **Adaptations to consent**

34
35 195 The requirement to reduce face-to-face contact with participants meant that, although consent
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37 196 remained a requirement, this process had to be managed virtually with the HCP on the video call
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39 197 and participants completing and signing an online form. In line with the drive for research to be
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41 198 enabled by digital tools[14], this data is now captured straight into Qualtrics (online system)
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43 199 which is directly accessible by the research team. This allowed more efficient and accurate data
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45 200 handling without the need to transfer data from paper to database. In general, this worked well,
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47 201 however there were some cases where it did not, primarily because patients were unable to
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49 202 access both Microsoft Teams and Qualtrics simultaneously.
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204 **Changes to the intervention - prescription and development of isometric exercise training**

205 The IE intervention used is a wall squat (Figure 1) protocol, which involves leaning against a
206 wall and squatting at an individual specific (knee joint) angle prescribed to elicit the required
207 exercise intensity based upon HR [22].

209 Figure 1. Isometric wall squat exercise

210
211 To accurately prescribe an individual specific wall squat angle, participants must complete at
212 least three-stages of a five-stage incremental isometric exercise test (IIET)[23]. It was originally
213 intended to subjectively pre-assess each patient's physical ability to meet this requirement during
214 the initial face-to-face screening visit. However, since this was replaced with a remote screening
215 visit, it was not possible to complete this capability assessment in person. As such, we had to
216 develop a simple protocol to be completed remotely via video call. This protocol tested the
217 participant's ability to reach an approximation of their personalised IE training angle and hold
218 for 60-seconds. The easy-to-follow instructions allow participants to carry out the test
219 independently. Delivering the test remotely required additional risk assessment, the translation of
220 safety considerations into the home (e.g. a nearby chair for support), along with additional online
221 instructional materials.

222
223 The IIET stayed the same apart from the time delay of having to establish the status of the
224 exercise type as non-aerosol generating; expert consensus from the Physiological Society was
225 not available until 20th May 2020[24]. However, new personal protective equipment (PPE)
226 considerations had to be implemented immediately in line with government guidelines[25]. This

227 had numerous implications, not least equipment costs and additional time considerations during
228 face-to-face testing.

229

230 **Impact of COVID-19 on NHS primary care staff participation**

231 It was originally planned to recruit 2-4 primary care sites in the Southeast based upon feasibility
232 searches performed before the pandemic. Between November 2019 and February 2020, one site
233 had committed in principle as a research site. The onset of COVID-19 and unprecedented
234 demands on the NHS, in particular primary care, led to initial difficulties in identifying principal
235 investigators at prospective sites due to uncertainty of workload. Identification of appropriate
236 HCPs with the capacity to deliver the intervention was already a challenge. This was exacerbated
237 by the fact that GP principal investigators were focused on the COVID-19 response and, later,
238 COVID-19 intervention studies and vaccination.

239

240 Embedding clinical research in the NHS is a key theme in the vision of *The Future of UK*
241 *Clinical Research Delivery*[14]. To create a research-positive culture in which all health and care
242 staff feel empowered to support and participate in clinical research as part of their job role, much
243 greater funding and resourcing of primary care would be necessary. To try and mitigate this in
244 the current study we were forced to approach sites further afield and would strongly recommend
245 over-planning the number of sites in future exercise-based studies.

246

247 **Conclusions**

248 Delivery of clinical trials in a safe and reliable way has always been complex, requiring good
249 governance and ethical frameworks, as well as robust infrastructure. Whilst there are many

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3 250 randomised controlled trials of exercise either published or planned, their use is more limited
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5 251 than conventional trials of medicinal products. In addition, there are barriers to the prescription
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7 252 of exercise by HCPs. These issues became more acute during the COVID-19 pandemic where,
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9
10 253 quite reasonably, trials directed at intervention in COVID-19 were prioritised[3]. However, it is
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12 254 evident that abandoning preventative healthcare measures has had (and more concerningly will
13
14 255 continue to have) a deleterious effect on the general population. In context, maintaining healthy
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16 256 lifestyle is important and this itself could be a protective factor during a pandemic like COVID-
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18 257 19 where patients with obesity and other risks factors were affected more.
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24 259 We have discussed several predictable hurdles the pandemic created for recruitment to a
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26 260 feasibility study of IE. Other unexpected problems have also arisen, such as a significant
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28 261 reduction in the number of people identified with stage 1 hypertension . Ironically, the pandemic
29
30 262 presented opportunities such as unprecedented speed and fluidity of change to the study
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32 263 approach. Remote consent and screening of patients, automated reminders, and video validation
33
34 264 of BP technique were all developed, approved and tested more rapidly as a result of necessity.
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36 265 However, this impacted directly upon our original commitment to ensure equality of access due
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38 266 to the associated IT requirements and level of IT literacy required to engage remotely e.g., need
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40 267 for webcams, two screens open etc. Overall, a willingness to constantly reflect and respond with
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42 268 protocol changes is essential in the current climate.
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49 270 Since we were unable to identify eligible patients through primary care, we sought and gained
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51 271 approval for direct marketing of the study resulting in a tremendous response (1362 click-
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53 272 throughs from 63 days of active social media advertising), indicating public willingness and
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273 enthusiasm for this type of research. Central databases, opt-in to research and direct marketing
274 (where appropriate) are likely to be much more effective methods for future study recruitment.

275
276 Finally, it may be worth considering a consensus statement from leaders in the field of exercise
277 research to find common ways to enhance recruitment to trials of exercise to augment current
278 clinical practice.

279
280 In closing, whilst this study is still ongoing due to the delays caused by COVID-19, it is evident
281 that we would not have been able to achieve our recruitment targets and the necessary data
282 collection without successfully implementing the changes discussed.

283

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375 **AUTHORS’ CONTRIBUTIONS**

376 Chris Farmer, Jim Wiles, Melanie Rees-Roberts, Jamie O’Driscoll and Douglas MacInnes
377 designed the original study concept and design. COVID-19 adaptations were implemented by
378 Chris Farmer and Jim Wiles as co-leads during COVID-19 and learnings collated by Ellie Santer
379 for this paper. The first draft of the manuscript was written by Chris Farmer, Jim Wiles, Ellie
380 Santer and further developed by Melanie Rees-Roberts, Alan West, John Darby. The paper was
381 then reviewed by Douglas MacInnes, Vanessa Short, Katerina Gousia, Tracy Pellatt-Higgins,
382 Rachel Borthwick, Tim Doulton and Jamie O’Driscoll. The study has two lay co-applicants
383 (Alan West and John Darby) who are involved as members of the research team and make shared
384 decisions on the study. Alan West and John Darby directly contributed to drafting and reviewing

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2
3 385 the content of this manuscript on Patient and Public Involvement during COVID. Pauline Swift
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5 386 is chair of the Study Steering Committee and with Tim Doulton reviewed drafts of this
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7 387 manuscript for clinical aspects within national context of hypertension treatment.
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31
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