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1 **The challenges of conducting a programme of ‘study within a trial’ (SWATs):**
2 **lessons from a paediatric setting**

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29

30 **Abstract**

31 **Background:** Randomised controlled trials are considered the best method for determining the
32 effectiveness and safety of health interventions. Trials involving children are essential to ensure that
33 treatments are safe and effective. However, many trials, both adult and paediatric, do not achieve
34 recruitment targets and/or maintain retention of participants, which can lead to a reduction in the
35 internal and external validity of the results. Identifying ways of improving trial efficiency are important
36 in order to increase the successful completion of trials.

37 **Main body:** A 'Study Within A Trial' (SWAT) is a self-contained study embedded within an ongoing
38 trial, which aims to establish evidence to improve the management and delivery of trials in healthcare.
39 There are increasing numbers of SWATs undertaken in recent years but very few within paediatric
40 trials and here we describe some of the challenges with undertaking a programme of SWATs within
41 paediatric clinical trials in the UK. The TRECA (TRials Engagement in Children and Adolescents) study
42 involves developing multimedia websites to use within paediatric trials to provide recruitment
43 information to children, young people and their families about the clinical trial. Challenges
44 encountered included governance issues such as host trial approval processes and sharing of
45 anonymised data; funding issues for host trials; internet quality and accessibility within the healthcare
46 setting; and ethical concerns associated with SWAT methodology. We believe the ethical concerns are
47 more pronounced in the paediatric setting, perhaps because fewer SWATs are undertaken there or
48 that a more cautious, risk-averse approach to undertaking research with children is taken.

49 **Conclusion:** SWATs are becoming increasingly common to provide an evidence base for methods for
50 improving trial efficiency. However, we encountered a number of unanticipated challenges to
51 embedding TRECA that have not been previously reported within the scientific literature. We believe
52 that if these issues were addressed, through wider promotion and explanation of undertaking SWATs

53 involving all key stakeholders, as well as exploration of alternative funding models for SWATs, this
54 would enable more streamlined, appropriate and timely processes for SWATs and enable a stronger
55 evidence base for what works to increase trial efficiency.

56
57 **Trial registration:** The TRECA study is registered on ISRCTN, ID 73136092. Registered on 24 August
58 2016.

59
60 **Key words:** ‘Study Within A Trial’ (SWAT), embedded trials, methodology, challenges, randomised
61 controlled trials, paediatrics, governance

62
63 **Background**

64 *The need for evidence-informed trials*
65 Although randomised controlled trials (RCTs) are the gold standard for developing an evidence base
66 on the effectiveness of healthcare interventions, significant uncertainties exist about their design,
67 conduct and reporting, meaning that trials are often not efficient. For example, approximately 50% of
68 trials fail to achieve their original recruitment targets [1]. Poor recruitment and retention of trial
69 participants can be very costly [2] and contributes significantly to research waste [3, 4].

70
71 The UK government has highlighted its ambition to accelerate the development of innovative
72 medicines to improve patient health outcomes and healthcare efficiency [5]. However, without the
73 ability to accelerate the evaluation of healthcare innovations, and for these evaluations to be

74 completed to time and to target, this ambition will be stymied. Despite our focus on the UK, this issue
75 is faced by many health systems around the world.

76

77 *'Study within a Trial' (SWAT), an emerging field*

78 With the recognition that developing the evidence base for trials should be a priority, there has been a
79 recent international movement to improve the efficiency and successful delivery of trials through the
80 use of rigorous evaluation, adopting the 'Study Within A Trial' (SWAT) methodology. A SWAT is a 'self-
81 contained study that has been embedded within a host trial with the aim of evaluating or exploring
82 alternative ways of delivering or organising a particular trial process' [6]. For instance, in the UK the
83 Medical Research Council (MRC) funded the START (Systematic Techniques for Assisting Recruitment
84 to Trials) programme that successfully developed a conceptual, methodological and logistical
85 framework to improve recruitment through embedding SWATs of recruitment interventions in
86 multiple host trials, and developed reporting guidelines for recruitment SWATs [7, 8]. The Northern
87 Ireland Hub for Trials Methodology Research has established the SWAT Repository to facilitate SWATs
88 [9]. Trial Forge is another UK initiative, based in Scotland, that aims to increase the evidence base for
89 trial decision-making and in doing so, improve trial efficiency, and it recently published guidance for
90 what is a SWAT [6]. The current MRC-funded PROMoting THE USE of SWATs (PROMETHEUS)
91 programme [10] is building on the START initiative to make SWATs standard practice in clinical trials in
92 the UK by funding and facilitating the start of at least 25 SWATs across multiple teams in the UK.
93 Recently the UK National Institute for Health Research (NIHR) announced a new funding stream for
94 'Studies Within A Trial (SWATs)' in the Health Technology Assessment (HTA) Programme [11], which
95 has the potential to increase the number of trial teams likely to consider, and/or actively undertake
96 SWATs. In the Republic of Ireland, the Health Research Board – Trials Methodology Research Network
97 (HRB-TMRN), support and fund research teams to undertake SWATs to improve the efficient conduct
98 of future trials [12].

99 *Previously identified challenges with SWATs*

100 Despite the current focus on SWATs, a range of challenges to undertaking them have been identified.
101 Challenges for host trials include increased complexity and management burden; compatibility
102 between the host and embedded trials; and the impact of the embedded trial on host trial design and
103 relationships with collaborators [13]. For embedded trials, there are concerns that host trial
104 investigators might have strong preferences, limiting the control that embedded study investigators
105 have over their research, and also concerns about sample size limiting statistical power [13]. Other
106 identified challenges include cost; the resistance of the chief investigator or co-investigators; funding
107 for SWATs; and distraction and additional workload for research staff [14, 15].

108

109 *The TRECA Study, an example of a SWAT to evaluate a new recruitment intervention*

110 In this paper we discuss some of the challenges encountered within a programme of SWATs, the TRials
111 Engagement in Children and Adolescents (TRECA) Study [16], funded by the UK NIHR Health Services
112 and Delivery Research (HS&DR) Programme (14/21/21). TRECA is investigating a novel alternative to a
113 printed participant information sheet (PIS) for children, young people and their parents, when
114 approached about a clinical trial. This is an important opportunity to explore alternative methods of
115 providing information as many PIS documents are lengthy, difficult to understand and do not
116 incorporate visual elements [17-20]. In the first phase of the TRECA study, multimedia website
117 templates about paediatric clinical trials using text, pictures, animations and short video clips were
118 developed (unpublished data; J Martin-Kerry, P Knapp, K Atkin , P Bower, I Watt, C Stones, S Higgins, R
119 Sheridan, J Preston, D Horton Taylor, B Young) and user tested [21]. Phase two of TRECA began in late
120 2017 and involves adapting the multimedia websites for six paediatric clinical trials (host trials) using
121 trial-specific content and embedding the websites as recruitment tools within the host trials. There is a
122 lack of evidence on the effectiveness of multimedia for supporting decision-making about trials,
123 particularly in the paediatric setting. When host trials embed TRECA, the trial randomises those

124 approached about trial participation to one of three arms of TRECA so that each person approached
125 receives one of the following: the PIS only; the multimedia website only; or both the PIS and
126 multimedia website. We are interested in the impact of the multimedia websites on rates of
127 recruitment and retention to the six trials, as well as the quality of decision-making by families about
128 trial participation.

129

130 Despite much interest and enthusiasm for SWATs, and clear benefits for utilising them to evaluate
131 new methodological interventions within RCTs [6], we have encountered a number of challenges to
132 embedding TRECA within UK paediatric trials. Here we describe these challenges and suggest some
133 possible solutions that may enable SWATs to be undertaken more quickly and efficiently within a
134 pediatric context, or other settings where there is a perception of patient vulnerability or risk.

135

136 **Challenges faced by TRECA**

137 The main challenges encountered when engaging with potential host trials to embed TRECA fall under
138 four main categories: governance and approvals; funding; methodological/ethical concerns; and
139 internet access and quality.

140

141 *Governance and approvals issues*

142 A number of governance and approvals issues have been encountered when embedding TRECA within
143 host paediatric trials:

144

145 Within Phase two of TRECA, each of the six host trials had different approval processes to embed
146 TRECA. Some trials required their Trial Management Group (TMG) to formally approve collaboration.
147 Other host trials requested that a feasibility questionnaire be developed by TRECA and sent to all
148 potential host trial sites. The questionnaires were accompanied by information about TRECA in terms
149 of the practicalities of what would be involved if the host trial site was to embed TRECA. We sought
150 each site's approval and agreement with embedding TRECA through the completion of a set of
151 questions relating to the process of embedding TRECA. From this, the decision still rested with the
152 TMG which may have only met infrequently. One host trial required two sets of feasibility
153 questionnaires to be circulated to the trial sites – one prior to a decision by the host TMG about
154 embedding TRECA, and another following this decision. In our experience it has often taken three to
155 eight months from initial discussions with the potential host trial until the trial has made a decision
156 about embedding TRECA. This has had an important time-delaying impact on TRECA's timelines.
157 Crucially, TRECA could not begin developing the multimedia websites (given they are tailored to the
158 trial) until the decision was made by the host trial, and the delay then impacted on the development
159 and embedding of the websites (the tested recruitment intervention).

160

161 So that TRECA could evaluate the impact of the multimedia websites on recruitment, retention and
162 quality of decision-making, we require anonymised patient data from each host trial. To this end, we
163 developed a data sharing agreement. Whilst we expected that these agreements would be
164 straightforward, host trial sponsors have raised concerns about sharing even anonymised data, and
165 legal teams from the host trials' sponsors have reviewed and queried the agreements prior to signing.
166 In addition, recent changes in data protection with the recent General Data Protection Regulation and
167 Data Protection Act 2018 have also led to further concerns about sharing of anonymised data, and the
168 need for a transparent approach to informing participants about the sharing of their data between
169 organisations. One host trial noted that the sponsor of the host trial would not be signing the

170 agreement, and instead required each participating host trial site to sign an individual data sharing
171 agreement with TRECA, increasing the administration and workload substantially.

172

173 *Funding issues for trials embedding SWATs*

174 Another challenge encountered relates to funding. The NIHR Clinical Research Network (CRN) provide
175 funding to trials in the UK through the process of funding per participant recruited (accruals) for so-
176 called 'portfolio-adopted' research studies. The Portfolio comprises high quality clinical research
177 studies that are eligible for CRN funding and support. Recruitment data allows the allocation of
178 funding to the NIHR Local Clinical Research Networks (LCRNs) to direct NHS service support to sites.
179 Almost every trial we have approached about TRECA has asked or assumed that the host trial would
180 receive two sets of accruals – one for recruitment of their participants into the host trial, and the
181 second for those who were randomised to TRECA. However, the CRN considers this situation to be
182 'double-counting' as all of those recruited to the host trial would have been approached using one of
183 the arms of TRECA and an additional consent process for the SWAT is not required. However, we can
184 see the trial's view that by embedding TRECA they are introducing more workload, although the
185 TRECA team aims to reduce this burden as much as is practicable. Receiving additional funding for the
186 local CRN may provide an incentive for a trial to embed a SWAT, particularly for the recruiters, as this
187 funding may enable the CRN to support the trial team.

188

189 Another accrual issue relates to a potential host trial for TRECA that was not portfolio-adopted. This
190 particular host trial team thought that by embedding TRECA, which is an NIHR portfolio-adopted
191 study, they would then be able to access an NIHR research nurse through funding/accruals to
192 undertake recruitment for the host trial. However, under the current CRN process this was not
193 possible. This raises the question of whether another funding model would assist with recruiting trials
194 to undertake SWATs. A middle ground may be to provide a recruitment incentive for trials to

195 undertake SWATs but below the level of accrual/funding for recruiting a trial participant. Another
196 option is to utilise the PROMETHEUS [10] model
197 (<https://www.york.ac.uk/healthsciences/research/trials/research/swats/prometheus/>) with a flat rate
198 for a SWAT provided to the trial team.

199

200 *Confusion around embedded trial methodology and ethical concerns*

201 Trialists have often been unsure about the methodology and approvals of embedded trials. We sought
202 overarching research ethics and Health Research Authority (HRA) approvals for TRECA prior to
203 identifying and approaching potential host trials. In this overarching ethics application we sought (and
204 received) approval so that host trials do not need to explain TRECA or seek consent for those
205 approached about the host trial in order to be randomised within TRECA. This is because explaining
206 TRECA to those approached about the host trial and seeking consent to TRECA would be confusing and
207 may also confound the effect of the information intervention being tested in the SWAT. However,
208 trials have generally expressed concern about people not needing to consent to the embedded trial,
209 despite these concerns not being raised by research ethics committees or the HRA.

210

211 In addition, NHS Trust Research & Development (R&D) departments (these departments are located
212 within NHS sites and are responsible for granting approval for research studies being undertaken
213 locally) are often unclear of how to review and approve embedded trials, which causes delays. For
214 example, one trial initially reviewed the TRECA documentation as an embedded study and then
215 decided that TRECA would be reviewed as a stand-alone study and requested all documentation to be
216 sent again and reviewed. In addition, R&D departments were often unsure about which
217 documentation they needed to review and some had concerns about participants not consenting to
218 the SWAT (despite ethics approval for this process). These additional steps caused further delays in
219 embedding TRECA.

220

221 *Accessibility and quality of internet provision*

222 An unexpected challenge with undertaking a SWAT involving the delivery of a multimedia website
223 within the healthcare setting was the variation in wifi conditions and permissions at each National
224 Health Service (NHS) site. This proved challenging when developing the multimedia websites for host
225 trials as the Principal Investigator for one host trial was unable to view the websites due to internet
226 viewing restrictions at the hospital (the videos and animations are stored on a site which was blocked
227 at this particular hospital). Furthermore, some wifi was either too slow to load animations and videos
228 or could not be reliably accessed. We overcame this issue by providing affected sites with a tablet
229 computer that had an internet SIM card.

230

231 **Other learnings from the TRECA study**

232 Despite the challenges we faced with incorporating this programme of SWATs within six host trials, we
233 have encountered a number of positive experiences. There is a genuine interest in presenting
234 information about trials to families in a more engaging way and there has been a great deal of
235 enthusiasm for the multimedia websites created. We have also found RECs and the HRA to be very
236 supportive of us evaluating the use of multimedia websites as an alternative or supplement to printed
237 PIS documents. We have also developed a structured and quality method of creating multimedia
238 websites by working with host trials and a company that specializes in developing websites and
239 animation (Morph; www.morph.co.uk). For researchers wanting to implement SWATs in future, we
240 would recommend early engagement with all stakeholders (including trialists, sponsors, R&D
241 department staff) about incorporating a SWAT so that any concerns or queries are addressed early.
242 We would also factor in a lead time of six months for trials to sign the data sharing agreement.

243

244 **Conclusions**

245 SWATs have become increasingly popular, offering an opportunity to identify what works best when
246 undertaking trials [6]. In conducting Phase two of the TRECA study, we have identified and described a
247 number of governance, funding and methodological challenges when embedding a programme of
248 SWATs within host paediatric trials. There are a small number of publications describing challenges
249 with embedding SWATs [13-15]; however, some of the issues identified within the TRECA study have
250 not previously been described and this paper provides detailed information about the challenges
251 faced. We also are not aware of any publications about SWATs undertaken within paediatric trials, and
252 believe that some of the challenges we have experienced have a more marked impact in the paediatric
253 context and in other contexts where there is a perception of increased patient vulnerability or risk. For
254 example, a recent Cochrane review showed that only one of 68 trials evaluating strategies to improve
255 recruitment into RCTs had included a paediatric sample [22]. However, we believe that the challenges
256 we have identified within TRECA may be applicable to trials with other populations including trials
257 involving adults and are relevant for other researchers wishing to undertake SWATs in a variety of
258 trials and settings. We also acknowledge that the issue of internet quality and access will only impact
259 on SWATs that involve delivery of websites and not on other methods of information provision.

260

261 We believe that the identified challenges are able to be overcome, enabling a more streamlined and
262 proportionate approach to trials reviewing requests for SWATs. We suggest that increasing awareness
263 of SWATs more widely in the UK, such as through publications and presentations, and ensuring that
264 paediatric trialists are involved, would assist with some of the ethical concerns raised, such as
265 participants not needing to provide explicit consent for the SWAT. We feel that the ethical concerns
266 expressed by host trials for TRECA reflect that this study was undertaken in the paediatric setting
267 where there may be more caution about novel methods. It is important that all stakeholders are
268 involved in a process of increasing SWATs awareness, including members of ethical committees,

269 sponsor representatives, principal investigators, trial managers and coordinators, TMGs, CRN, R&D
270 officers, trial managers and coordinators at trial sites and clinical trial units.

271

272 We also feel that the provision of more guidance to NHS sites and trials about how to review a SWAT,
273 and identifying earlier whether the host trial is able to embed it, would be beneficial. Undertaking
274 feasibility with sites participating in a multi-centre trial takes considerable time to develop and
275 distribute the questionnaire, answer site queries, collate results and then await TMG review. In
276 addition, we have found that a number of R&D departments have not been familiar with SWAT
277 methods, how to review SWATs, or the order in which they should review and approve studies (i.e.
278 approval before or after the host trial). R&D departments ultimately approve the undertaking of
279 SWATs at sites and are often not involved in early discussions with trialists about including a SWAT.
280 Ensuring that R&D departments are more familiar with SWATs would streamline the process of
281 incorporation within new and existing trials. If these elements can be addressed, we would hope that
282 this would enable more SWATs to be undertaken, providing a stronger evidence base about what
283 works best in RCTs. In terms of funding models for host trials embedding a SWAT, we feel alternative
284 models should be explored to generate incentives for host trials that match the workload of
285 undertaking the SWAT, and the HTA funding stream may provide a viable funding alternative. We have
286 described the UK situation but feel that these issues of funding support to host trials may be similar in
287 other countries.

288

289 In summary, we suggest that the following actions may overcome some of the challenges with
290 undertaking SWATs in the paediatric setting:

- 291 1. Reduce ethical approval and governance barriers by increasing awareness of SWATs and engaging
292 all stakeholders (including ethical committees, sponsor representatives, principal investigators, trial
293 managers and coordinators, TMGs, R&D and trial sites).
- 294 2. Provide more guidance and explanation about SWATs. In the UK, this could be led by NIHR or HRA,
295 who are perhaps best positioned to provide the guidance and support.
- 296 3. Explore other funding models that may better support SWATs. This may be through a down-
297 weighted recruitment incentive for SWATs through the CRN, or using the PROMETHEUS model of
298 providing a set amount to trial teams for undertaking a SWAT, or using the new HTA funding stream.
- 299 4. Review existing internet access in hospitals to determine whether improved access can be enabled
300 to allow interventions such as multimedia websites about trials or healthcare treatments to be
301 accessed more easily.

302

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360

361 **List of abbreviations**

362 **HRA:** Health Research Authority

363 **HRB-TMRN:** Health Research Board – Trials Methodology Research Network

364 **HS&DR:** Health Services and Delivery Research

365 **HTA:** Health Technology Assessment

366 **MRC:** Medical Research Council

367 **NHS:** National Health Service

368 **NIHR:** National Institute for Health Research

369 **RCT:** randomised controlled trial

370 **R&D:** Research and Development

371 **START:** Systematic Techniques for Assisting Recruitment to Trials

372 **SWAT:** 'Study Within A Trial'

373 **TRECA:** TRials Engagement in Children and Adolescents

374 **TMG:** Trial Management Group

375

376 **Declarations**

377 **Ethics approval and consent to participate**

378 Approval was received from the Yorkshire & The Humber - Bradford Leeds Research Ethics Committee

379 (17/YH/0082) and the Health Research Authority (IRAS ID 212761) to embed TRECA within six

380 paediatric trials in the UK.

381

382 **Consent for publication**

383 Not applicable

384

385 **Availability of data and material**

386 Not applicable

387

388 **Competing interests**

389 The authors declare they have no competing interests.

390

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396

397 **Authors' contributions**

398 JM-K initially discussed the writing of some of the challenges within TRECA with PK, PB and IW. This
399 led to a meeting with co-authors to discuss the development of this manuscript. JM-K led the writing
400 of this manuscript with sections of the background written by AP. IW provided early input into the
401 draft with ST, PK, PB, DT, CA contributing to later drafts; and all authors critically reviewed and revised
402 the manuscript. All co-authors approved the final version of the manuscript.

403

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