

A Factorial Randomised Controlled Trial embedded within the FLexor repAir and REhabilitation (FLARE) trial investigating the effect on recruitment rates of an Enhanced Associate Principal Investigator Training Package and Additional Digital Nudge delivered by a Trial Coordinator

1. BACKGROUND

1.1 Introduction

Randomised controlled trials (RCTs) are considered the gold standard when evaluating the efficacy and effectiveness of health care interventions. Unfortunately, many RCTs struggle with recruitment and fail to reach their target sample size. This can lead to an under powered trial and jeopardise the validity of the reported results.

1.2 Recruitment

The challenge of recruitment to RCTs is well documented.^{1,2} In the UK, only 55% of National Institute of Health Research (NIHR) funded trials run between 2002 and 2008 met their recruitment target, with 45% needing funding extensions.³ A cohort study of 114 trials (MRC and HTA-funded) found that only 31% achieved the original recruitment target, and 53% had to be extended.⁴ Many trials have also closed prematurely due to recruitment problems.^{4,5,6} A survey of Clinical Trials Units (CTUs) in the UK found that recruitment remained their priority.⁷

Many interventions to improve recruitment at sites, such as site champions and incentivising clinicians with non-financial benefits are routinely used but do not have any evidence of their effectiveness. One way to provide a rigorous evaluation and evidence is to conduct a Study Within a Trial (SWAT)⁸ such as this.

A systematic review of incentives and disincentives for clinicians to recruit to RCTs identified no RCTs of interventions hence highlighting the need for further work in this area.⁹

1.3 Plastics and Hand Surgery Research

Hand and Plastic Surgery research output is improving, with more priority being placed on the formation of high-quality research. Methods for this include the modification of Certification of Completion of Training (CCT) criteria to include research targets, formation of trainee collaborative research networks and cohort studies with multicentre collaborators to provide a framework for RCT recruitment. Considering the network of trainees in hand and plastic surgery units nationally, interventions directed at trainee recruitment has the potential to improve the performance of clinical trials in this area.

1.3.1 Associate Principal Investigator

The NIHR supported Associate Principal Investigators (API) scheme aims to integrate clinical research as part of routine clinical training by developing a structure for APIs to work alongside the local Principal Investigators (PIs) to gain experience in local leadership of clinical trials, supported by mentors. This allows recognition for junior doctors, nurses, and allied health professionals' engagement in a standardised and consistent manner across all NIHR portfolio trials.

The role can help co-ordinate and engage local trainees in recruiting patients to the trial especially out of normal working hours. Several multicentre trials have utilised APIs at recruitment centres with anecdotal patient recruitment success. However, there are also possible detrimental effects on recruitment from APIs being utilised e.g., replacement or dilution of trained research nurses, increased protocol deviations and slower recruitment.

In standard practice, an API is recruited and managed locally by the site PI. The API manual

developed by the CTU and API Toolkit developed by the NIHR serve as resources to guide delivery of their role as an API. There is therefore potential to create an enhanced API training and support package where formal initial education and ongoing support can be used to support the API with a view to enhancing their knowledge and confidence in undertaking their role. A systematic review of training programmes for recruiters to RCTs found that these programmes were well received and increased recruiters' self-confidence¹⁰, but did not investigate the impact on patient recruitment rates. The review found limited high-quality evidence for training interventions aimed at recruiters and suggested that there is a need to develop more robust designs, especially randomised or cluster randomised trials to assess the effectiveness of training programs.

1.3.2 Nudging

The behavioural concept of nudge theory is a way of influencing an individual's behaviour through an intervention without limiting their choice¹¹. This concept is used extensively in marketing, economics and healthcare promotion.

Digital nudging is used regularly in RCTs e.g., emails, recruitment league tables circulated to recruiting sites, and encouragement emails; however, there is limited evidence regarding the effect of these interventions on recruitment. A key point at which to reinforce recruitment behaviour is just after successful recruitment of a person to a trial.

An additional email communication to recruiting staff, following a successful recruitment to a trial incorporating features such as personalisation, appreciation for work done, and praise sent to the recruiter in a timely manner may positively reinforce the behaviour of recruiting to the trial.

However, this does increase the burden of emails sent to trained research staff who are experienced in recruitment to trials. Consequently, this may have the unintended effect of annoyance and irritation leading to poorer recruitment.

If deemed successful, elements of this intervention can be incorporated into the automatic email sent to sites, and trial units could consider the resource allocation needed to deliver this additional email intervention when planning future RCTs. Recently, Agni et al.¹² conducted a factorial design SWAT embedded within the WHITE Coral 8 RCT to investigate the effect of an Enhanced API Training Package and Additional Digital Nudge on recruitment rates (SWAT Repository number 67). The results suggest that there is a statistically significant benefit to trial recruitment of an enhanced training and support package for APIs delivered by a surgical trainee, though no evidence of benefit from a digital nudge intervention¹³. A recommendation from the published results is that the intervention should be evaluated in a SWAT using a CTU member delivering the intervention, as this is more likely to be deliverable at scale than delivery by a surgical trainee. The earlier SWAT was undertaken as part of a doctoral programme of work and subsequently explored in another SWAT embedded in the Simple Olecranon Fracture Fixation Trial (SWAT Repository number 140) and it is unlikely that outside this context, it would be feasible to recruit a surgical trainee to undertake this role during the timeframe of a surgical trial.

This proposed SWAT therefore is similar to earlier SWATs, with the intervention delivered by a Trial Coordinator, conducted within the FLARE RCT. This will allow the results to be combined in a meta-analysis increasing the power of the analysis. Given the blinding procedures within the FLARE host trial, only surgical trainee APIs will be randomised into the SWAT.

2. Trial of recruitment intervention

2.1 Aim

This SWAT will utilise a 2x2 factorial design, embedded within the FLARE trial to evaluate the effect

on recruitment rates in a secondary care setting of two interventions: Enhanced Associate Principal Investigator Package; and Digital Nudging. For the purpose of this SWAT, consent is used as a measure of recruitment, due to blinding procedures within the FLARE host trial.

2.2 OBJECTIVES

Primary

The primary objective of this SWAT will be to assess the effectiveness of an Enhanced API training package, a digital nudge, and a combined intervention, compared to standard practice API and/or standard consent processes, on the total number of patients consented to the FLARE trial in the 6-month period that the API is in post at a recruiting site.

Secondary

Secondary objectives include:

- Assess the effectiveness of an Enhanced API training package, a digital nudge, and a combined intervention on the total number of patients consented to the FLARE trial over a 12-month period (during 6 months of an API intervention and 6 months after) at a recruiting site.
- Compare the proportion of eligible participants who are consented.
- Determine the amount of Trial Coordinators time taken to deliver the enhanced API training package and detail the methods of additional contact for peer support of the APIs.

2.3 INTERVENTIONS

The standard method of identifying patients for recruitment to FLARE is via screening patients at Accident and Emergency units and trauma meetings attended by a multidisciplinary team, usually including consultants, physiotherapists, surgical trainees, and the research team at site. APIs are used at many recruitment centres routinely already.

Standard practice for supporting APIs

The API receives a standard checklist from the NIHR once they join the scheme and they are emailed a role specific manual from the CTU. Beyond this, there is no further contact from the CTU directly with the API, other than contact as part of the whole recruiting team, such as site initiation visits or site notifications.

Standard practice - successful recruitment of a participant

The site team member obtaining informed consent will complete the process via REDCap, as detailed in the FLARE Trial protocol and Trial Site Manual. The randomiser will receive standard confirmation of randomisation on the REDCap screen at the time of randomisation. Site teams do not receive any automated emails about consent, randomisation, or allocated treatment.

2.3.1 Enhanced Associate Principal Investigator package

The Enhanced API intervention will be a complex intervention involving:

1. **EDUCATION:** 1:1 telephone or video conference training delivered by a member of the YTU team to the API covering:
 - a. Background to FLARE
 - b. API role and benefits of participating in the scheme
 - c. How to effectively perform the API Role
 - d. How to recruit and randomise to FLARE

2. **SUPPORT:** Support and advice through follow up emails and telephone calls to a member of the CTU team if required for problems related to carrying out the role.
3. **DIGITAL SUPPLEMENTARY INFORMATION:** Provision of supplementary material by email including:
 - a. FLARE specific API manual containing information on the roles of a PI and API, method of consent and randomisation, benefits to the trainee of participating in the role, and relevant guidance on mental health and research legislation relevant to recruiting participants.
 - b. Induction summary presentation

The educational session will be an induction into the API role run by a member of the YTU team (FLARE Trial Coordinator). It will be an approximately 40-minute telephone/videoconference session covering all aspects of the role, with additional supplementary material sent one week before the induction time slot. The APIs will be emailed monthly to ask if there are any problems with recruitment that they need support with. A record of these communications will be kept by YTU in an API log.

2.3.2 Digital Nudging

The second intervention will be a Digital Nudge email from a member of the YTU team (FLARE Trial Coordinator). An email will be sent to the API each time a participant is consented by the API as a FLARE team member, identified by their name on the REDCap consent form (see Appendix 1). Each email will include the following:

- Personalisation (first name of consenter)
- Encouragement through praise to continue consenting drawn from a matrix of statements

(Appendix 2).

- Statement of appreciation for consenting a patient to FLARE.

The aim will be to send this email to the site team within 72-hours of receiving the notification of consent at YTU. Where multiple participants have been consented in the 72-hour period and multiple consent forms received, only one email will be sent referring to the number completed in the period. This will reduce the burden of emails sent to research staff.

2.3.3 Intervention Summary

The activity for each intervention is summarised below for ease of reference (Table 1)

Table 1: Summary of trial intervention activity

<u>ACTIVITY</u>	<u>STANDARD PRACTICE</u>	<u>ENHANCED API</u>	<u>DIGITAL NUDGE</u>
Identify API for the trial	Local Principal Investigator	Local Principal Investigator	
Training of API regarding how to perform their role	Local Principal Investigator FLARE API Manual	Local Principal Investigator 1:1 telephone/ videoconference induction by Trial coordinator FLARE API manual Induction summary presentation	
Training API regarding the FLARE Trial and consenting procedures	Local Principal Investigator	Local Principal Investigator 1:1 telephone/ videoconference induction by Trial Coordinator	
Peer Support of API		Monthly contact by Trial Coordinator working on FLARE from YTU.	

Digital information provided to API	FLARE API Manual	FLARE API manual Induction summary presentation	
Identifying patients for the trial	A&E/Trauma meeting	A&E/Trauma meeting	
Confirmation of consent	Standard completion of consent form via REDCap		Personalised email sent to the API. Email will be sent each time a consent has been completed by the API as the FLARE team member (identified by their name on the REDCap)

2.4 TRIAL DESIGN

This will be a multi-centre, 2x2 factorial randomised controlled trial embedded in the FLARE randomised controlled trial.

Randomisation will be undertaken initially for all sites with a confirmed surgical trainee API, which are participating in the study at the point of the trial opening, with any additional sites randomised as they open to recruitment and have a surgical trainee API confirmed. The interventions will run for six months in each recruitment centre; this is due to the length of time an API surgical trainee would usually be in place at the site. The collection of data for this SWAT will run for 12 months in each recruiting centre. As randomisation is conducted at site level, any surgical trainee APIs who join the team after the site has been randomised will receive the same intervention, however their data will not be included in the SWAT. Any potential contamination, caused by APIs moving to a recruiting site that is not randomised to receive the enhanced intervention will be monitored using site delegation logs.

The factorial design will allow for the evaluation of two interventions in one trial thus presents a more cost-effective option than running two separate SWATs.¹⁴ There is potential for interaction between the two interventions, and this will be explored in the analysis.

There will be four groups in this SWAT (see Table 3):

- Group A – Standard consent procedures and Enhanced API Intervention
- Group B – Standard consent procedures **and** Digital Nudge intervention **and** Enhanced API Intervention
- Group C – Standard consent procedures and standard practice API
- Group D – Standard consent procedures **and** Digital Nudge Intervention **and** standard practice API

Table 3: Factorial Design of the trial

		API		Digital Nudging Comparison
		(Intervention) Enhanced API	(Control) Standard practice API	
Digital	(Control) Standard consent	Group A <i>Standard consent and enhanced API intervention</i>	Group C <i>Standard consent and standard practice API</i>	A+C
	(Intervention) Standard consent + Digital Nudging	Group B <i>Standard consent and digital nudge intervention and enhanced API intervention</i>	Group D <i>Standard consent and digital nudge intervention and standard practice API</i>	B+D
	Enhanced API Comparison	A+B	C+D	

2.5 OUTCOME MEASURES

Primary Outcome

The primary outcome is the total number of patients consented to FLARE by a site in the first six months that the surgical trainee API is in place. This data will be collected from REDCap.

Secondary Outcomes

1. The total number of patients consented to FLARE by a site over a 12-month recruitment period (during 6 months of a surgical trainee API intervention and 6 months after).
2. The proportion of eligible patients who were consented to the trial by a site in the first six months that the surgical trainee API is in place, and in the months 7 - 12 following the surgical trainee API being in place. It will be obtained using the informed consent data on REDCap, and the number of consents obtained recorded.
3. Time taken (in minutes) by Trial Coordinator to deliver the enhanced API training package and detail the methods of additional contact for peer support of the surgical trainee APIs.
4. Estimated cost of implementing the interventions at a site.

2.6 PARTICIPANTS

All centres recruiting to FLARE who have a confirmed surgical trainee API will be included. This SWAT does not directly involve patient participation. Sites are aware of the SWAT, as it is described in the host trial protocol, however sites are unaware of their randomised allocation.

2.7 RANDOMISATION

The FLARE centres open to recruitment who have a confirmed surgical trainee API will be randomised 1:1:1:1 by minimisation to one of the four groups to balance key baseline characteristics. A statistician at YTU will undertake the minimisation using the software MinimPY.¹⁵ The minimisation will be undertaken initially for all sites with a confirmed surgical trainee API, which are participating in the study at the point of the trial opening, with any additional sites randomised as they open to recruitment and have a surgical trainee API confirmed. Although sites are aware of the SWAT, concealment of the SWAT allocation reduces the risk of subversion or predictability.

Naïve minimisation with base probability 1.0 will be used to ensure balance of factors between allocations. The minimisation will include the following factors:

1. Site size (large site vs small site based on population they serve)
2. Previous recruiting time (site open for <2 months vs site open for ≥ 2 months; at the point the surgical trainee API is confirmed and the site are randomised into the SWAT).

2.8 SAMPLE SIZE

Since this is an embedded SWAT, the sample size of sites is constrained to the number of centres who have a surgical trainee API in post. This is anticipated to be at least 18 sites.

2.9 STATISTICAL ANALYSIS

All analyses will be conducted in Stata v17 (or later) on an ITT (intention to treat) where all sites are included in the group they were allocated. Statistical significance will be assessed using two-sided statistical tests at the 5% significance level. The trial will be reported to CONSORT guidelines, and a flow diagram will present the progression of sites through the trial.

Baseline data relating to the sites (including the minimisation factors) will be summarised for the four groups (A - D as listed earlier); and for the comparison groups (i.e., Enhanced API (A + B), standard API (C + D), digital nudge (B + D) vs standard practice (A + C)). Continuous data will be presented using descriptive statistics (e.g., mean, standard deviation), while categorical data will be given as counts and percentages. No formal statistical comparison of baseline data will be undertaken between the groups.

The number of participants consented will be summarised overall, as well as for each arm of the SWAT. A Poisson regression model, containing the two interventions (Enhanced API **and** Digital

Nudge) and the minimisation factors (site size, and number recruited prior to SWAT implementation be included in their continuous form) will be performed. Adjusted incidence rate ratios (IRRs) and associated 95% confidence intervals (CIs) will be obtained from this model. The presence of an interaction between the two interventions will also be tested by re-running this model including an interaction term; this will be assessed at 10% significance level. The total number of consents will be analysed in a similar way. The proportion of eligible patients consented will be analysed using a logistic model, adjusting for the same factors as in the primary analysis.

Feasibility outcomes, such as the time required to run the education intervention and communication time and methods used for the peer support aspect of the intervention, will be reported descriptively.

If possible, an Individual Participant Data (IPD) meta-analysis combining the results of this SWAT with the results of the previous SWAT will be performed.

3. ETHICS

The study is embedded under the main FLARE trial which has been approved by REC (REC ID: 23/NW/0004)

4. REGISTRATION, PUBLICATION and DISSEMINATION

This study is embedded in the FLARE Trial (ISRCTN10918157), and the trial will be registered to the SWAT repository store as part of the Northern Ireland Hub for Trials Methodology Research. Results of this study will be published in a peer-reviewed journal and be shared with hospital sites.

5. FUNDING

FLARE is funded by National Institute of Health Research (HTA Project: NIHR133784) and funding for the conduct of this SWAT was included in the grant.

REFERENCES

1. Puffer S, Torgerson D, Watson J. Evidence for risk of bias in cluster randomised trials: review of recent trials published in three general medical journals. *BMJ*. 2003;327(7418):785-789. doi:10.1136/bmj.327.7418.785.
2. Sully BGO, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: A review of trials funded by two UK funding agencies. *Trials*. 2013;14(1). doi:10.1186/1745-6215-14-166.
3. Treweek S, Altman DG, Bower P, et al. Making randomised trials more efficient: report of the first meeting to discuss the Trial Forge platform. *Trials*. 2015;16(1):261. doi:10.1186/s13063-015-0776-0.
4. McDonald AM, Knight RC, Campbell MK, et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials*. 2006;7. doi:10.1186/1745-6215-7-9.
5. Foy R, Parry J, Duggan a, et al. How evidence based are recruitment strategies to randomized controlled trials in primary care? Experience from seven studies. *Fam Pract*. 2003;20(1):83-92. doi:10.1093/fampra/20.1.83.
6. Bower P, Wilson S, Mathers N. Short report: How often do UK primary care trials face recruitment delays? *Fam Pract*. 2007;24(6):601-603. doi:10.1093/fampra/cmm051.
7. Tudur Smith C, Hickey H, Clarke M, Blazeby J, Williamson P. The trials methodological research agenda: Results from a priority setting exercise. *Trials*. 2014;15(1). doi:10.1186/1745-6215-15-32.
8. Rick, J., Clarke, M., Montgomery, A.A., Brocklehurst P., Evans, R. and Bower, P. (2018) Doing

- trials within trials: a qualitative study of stakeholder views on barriers and facilitators to the routine adoption of methodology research in clinical trials. *Trials*. 19:481.
9. Treweek S, Lockhart P, Pitkethly M, et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ Open*. 2013;3(2):e002360. doi:10.1136/bmjopen-2012-002360.
 10. Townsend D, Mills N, Savović J, Donovan JL. A systematic review of training programmes for recruiters to randomised controlled trials. *Trials*. 2015;16(1). doi:10.1186/s13063-015-0908-6.
 11. Cabinet Office Behavioural Insights Team. Applying Behavioural Insights to Organ Donation: preliminary results from a randomised controlled trial. 2013:1-11. papers2://publication/uuid/AF229C81-AD21-44D7-851F-CBC015DB96B7.
 12. Agni, N., Fairhurst, C., McDaid, C., Reed, M. and Torgerson, D., 2019. Protocol for a factorial randomised controlled trial, embedded within WHiTE 8 COPAL, of an Enhanced Trainee Principal Investigator Package and Additional Digital Nudge to increase recruitment rates. *F1000Research*, 8.
 13. Agni, N.R., Fairhurst, C., McDaid, C., Reed, M.R. and Torgerson, D.J., 2022. EnTraP: A factorial randomised controlled trial embedded within world hip trauma evaluation eight COPAL investigating the effect of an enhanced trainee principal investigator package and digital nudge on recruitment rates. *Research Methods in Medicine & Health Sciences*, 3(2), pp.33-41.
 14. Montgomery AA, Peters TJ, Little P, et al. Design, analysis and presentation of factorial randomised controlled trials. *BMC Med Res Methodol*. 2003;3(1):26. doi:10.1186/1471-2288-3-26.
 15. Saghaei, Mahmoud & Saghaei, Sara. (2011). Implementation of an open-source customizable minimization program for allocation of patients to parallel groups in clinical trials. *Journal of Biomedical Science and Engineering*. 4. 734-739. 10.4236/jbise.2011.411090.

Appendix 1: Nudge email text

To be sent to the consentor:

Dear *(insert first name)*,

(Encouragement Word– random from table 1) for consenting *(subject(s) -xxxxx)* to the FLEXor repAir and Rehabilitation (FLARE) Trial.

(Statement of appreciation – random from table 2) in consenting this/these patient(s) to the trial as we understand the difficulty and pressures of accommodating this during your busy day.

Your participation gets us one step closer to the target sample size of 310 patients and we would be grateful if you would continue to consent patients as the opportunity arises.

Keep up the good work,

[add digital signature of FLARE YTU team member and FLARE Co-Chief Investigators]

Table 1: Encouragement words

Brilliant work	Incredible work
Excellent job	Outstanding job
Superb job	Tremendous work
Fantastic work	Awesome job
Amazing job	Exceptional job

Table 2: Statement of appreciation

We thank you for your effort
We appreciate your commitment
We thank you for your hard work
We appreciate your effort
We value your contribution
We highly regard your contribution

Appendix 2: Nudge Matrix

NUDGE MATRIX

- Personalisation (first name of consenter)
- Encouragement through praise to continue consenting (Conroy et al 2009, thesis)
 1. Brilliant
 2. Excellent
 3. Superb
 4. Fantastic
 5. Amazing
 6. Incredible
 7. Outstanding
 8. Tremendous
 9. Awesome
 10. Exceptional
- Statement of appreciation for consenting a patient to FLARE
 1. We thank you for your effort
 2. We appreciate your commitment
 3. We thank you for your hard work
 4. We appreciate your effort
 5. We value your contribution
 6. We highly regard your contribution
- Digital nudge within 72 hours after consent

Deci, E. L., & Ryan, R. M. (1987). The support of autonomy and the control of behavior. *Journal of personality and social psychology*, 53(6), 1024.

Rosenfeld, L. B., & Richman, J. M. (1999). Supportive communication and school outcomes, Part II: Academically “at-risk” low income high school students. *Communication Education*, 48(4), 294-307.

Castleman (2013), Summer Nudging: Can Text Messages and Peer Mentor Outreach Increase College-Going Among Low-Income High School Graduates?