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Increase in recruitment upon integration of trial into a clinical care pathway: an observational study

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ABSTRACT

Introduction Many respiratory clinical trials fail to reach their recruitment target and this problem exacerbates existing funding issues. Integration of the clinical trial recruitment process into a clinical care pathway (CCP) may represent an effective way to significantly increase recruitment numbers.

Methods A respiratory support unit and a CCP for escalation of patients with severe COVID-19 were established on 11 January 2021. The recruitment process for the Randomised Evaluation of COVID-19 Therapy-Respiratory Support trial was integrated into the CCP on the same date. Recruitment data for the trial were collected before and after integration into the CCP.

Results On integration of the recruitment process into a CCP, there was a significant increase in recruitment numbers. Fifty patients were recruited over 266 days before this process occurred whereas 108 patients were recruited over 49 days after this process. There was a statistically significant increase in both the proportion of recruited patients relative to the number of COVID-19 hospital admissions (change from 2.8% to 9.1%, p<0.0001) and intensive therapy unit admissions (change from 17.8% to 50.2%, p<0.001) over the same period, showing that this increase in recruitment was independent of COVID-19 prevalence.

Discussion Integrating the trial recruitment process into a CCP can significantly boost recruitment numbers. This represents an innovative model that can be used to maximise recruitment without impacting on the financial and labour costs associated with the running of a respiratory clinical trial.

Key messages

- How can recruitment into respiratory clinical trials be improved without significantly increasing financial and labour costs?
- Integration of a respiratory trial recruitment process into a clinical care pathway is an innovative model to significantly boost recruitment into the trial.
- We have managed to demonstrate an effective model at boosting recruitment into a respiratory clinical trial that can be applied in a demanding clinical setting, allowing significant financial and labour cost minimisation.

INTRODUCTION

Clinical trials and their generated results are crucial. However, a common problem facing clinical trials is the poor recruitment of eligible participants. In particular, 26.3% of respiratory trials fail to recruit to their target sample size,[1] leading potentially to underpowered study results. Respiratory disease research is comparatively less well funded than other disease areas[2] and poor recruitment further exacerbates this problem often leading to trial extensions or failures. Patients themselves potentially miss out on indirect benefits as those cared for in research-active hospitals experience better health outcomes even if they are not directly involved in clinical trials themselves.[3]

Multiple barriers that lead to poor clinical trial participation have previously been identified. First, many healthcare centres may lack a structured and organised screening process which makes identifying potential participants difficult.[4] Second, the lack of resources allocated to research in healthcare organisations means that less time and manpower is allocated to screen for participants.[4 5] Third, patient factors such as fears related to risks of untested interventions, distrust in research and difficulty in understanding the importance of randomisation also impact on recruitment success.[4 6]

Clinical care pathways (CCPs) are multidisciplinary tools aimed at standardising care processes to improve patient outcomes. Traditionally, results from clinical trials are used to inform clinical guideline recommendations and in turn, CCPs integrate these guidelines within local healthcare organisations. In this letter, we describe the recruitment into the

Randomised Evaluation of COVID-19 Therapy – Respiratory Support (RECOVERY-RS) trial[7] before and after integration into the local CCP in a single tertiary hospital setting.

METHODS

RECOVERY-RS is a UK-wide clinical trial assessing the efficacy of non-invasive respiratory support against standard care for patients with severe COVID-19.[7] Patients are randomised in a 1:1:1 ratio to receive either continuous positive airway pressure (CPAP), high-flow nasal oxygen (HFNO) or standard care (oxygen delivered by face mask or nasal cannula). Recruitment to the trial commenced at the Queen Elizabeth Hospital Birmingham (QEHB), UK on 20 April 2020. Initially at QEHB, patients with severe COVID-19 were not initiated on non-invasive respiratory support outside the intensive care environment due to the lack of evidence supporting these interventions, and risks associated with aerosol generating procedures. Eligible patients were therefore recruited on an ad-hoc basis by research teams from general medical and respiratory wards; dependant on the parent team being aware of the trial and capacity in the intensive therapy unit (ITU).

On 11 January 2021, in response to guidance released by the British Thoracic Society and the Intensive Care Society,[8] a respiratory support unit (RSU) was established to provide enhanced respiratory support for patients with severe COVID-19 outside the intensive care environment. Part of a respiratory ward was reconfigured to accommodate eight high-dependency beds with a 1:4 nurse-to-patient ratio. Patients on RSU were continuously monitored, supported by twice-daily consultant-led reviews and regular input from the intensive care team. A CCP was developed for the escalation of patients with COVID-19 on general wards to RSU.

Recruitment into RECOVERY-RS was integrated into the RSU CCP on the same day that the unit was established (11 January 2021). On each day, patients with COVID-19 who met the inclusion criteria for recruitment into the trial were identified using the local in-house built electronic health record system. These patients were assessed by the daily nominated RSU consultant and if eligible, participation in the trial was discussed. If the patient consented to participate in the study, they were randomised into one of the treatment arms and transferred to either RSU or the respiratory ward for treatment initiation (see figure 1). The RECOVERY-RS trial took a pragmatic approach to the consent and randomisation process taking into account the severity of illness of the patients involved, as well as the clinical and time pressures that recruiting sites were under during the recruitment period. Verbal consent from the patient was accepted with simplified patient information leaflets available minimising the amount of text the patients had to read. Patients who declined participation into the trial were also transferred to the same ward and received the same care as those randomised to the standard care arm of RECOVERY-RS.

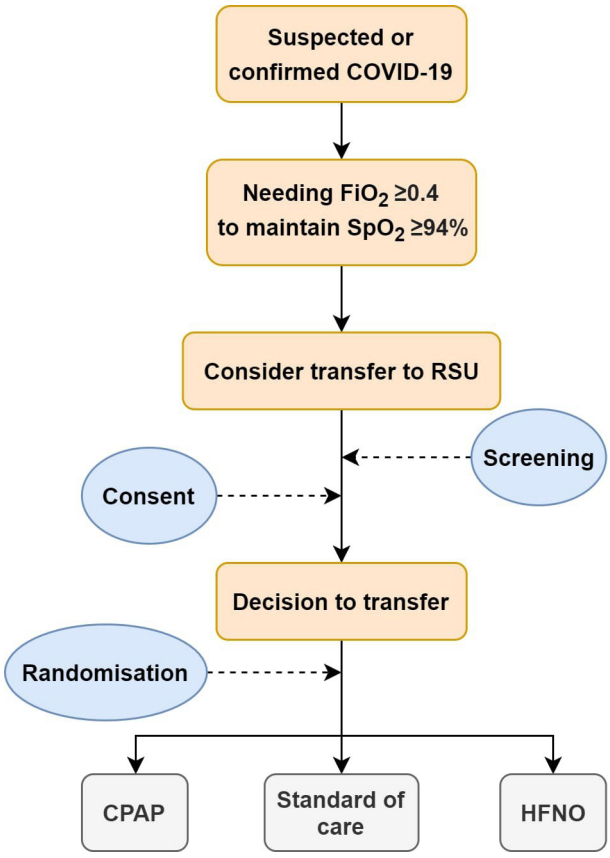

Figure 1 Flow diagram illustrating how recruitment into the Randomised Evaluation of COVID-19 Therapy-Respiratory Support trial was integrated into the respiratory support unit (RSU) clinical care pathway. Patients with COVID-19 who needed fractional inspired oxygen (FiO_2)≥0.4 to maintain oxygen saturations ≥94% were considered for escalation to RSU for further management. Identified patients were screened by the RSU-lead respiratory physician or critical care physician and approached for potential recruitment. If the patient consented, they were randomised to one of the treatment arms: Continuous positive airway pressure (CPAP), high flow nasal oxygen (HFNO) or standard of care. Patients who were randomised to receive CPAP or HFNO were transferred to RSU for initiation of treatment whereas patients who were randomised to the standard care arm or declined enrolment into the trial were transferred to the same respiratory ward, but not to the beds that comprised RSU. SpO2, oxygen saturation.

This was a retrospective service evaluation and as such did not require ethics approval.[9] This service evaluation has been registered with the Trust's Clinical Audit Registration and Management System (CARMS) and was given the reference number CARMS-17179. Recruitment data to the RECOVERY-RS trial were collected between 20 April 2020 and 28 February 2021. To assess whether changes in recruitment were independent of COVID-19 prevalence, the number of patients with COVID-19 disease admitted to the hospital and the number admitted to ITU were

Table 1 Monthly figures of inpatient admissions and ITU admissions from COVID-19 as well as recruitment into Randomised Evaluation of COVID-19 Therapy-Respiratory Support since the trial was opened. Only data from the 20th onwards are shown for the April 2020 month which reflects when the trial was opened in Queen Elizabeth Hospital Birmingham. The data for January 2021 was split into two (before 11th January and 11th January onwards) to reflect the opening of RSU

Month	Inpatient admissions	ITU admissions	Trial recruitment
April 2020 (20th onward)	91	13	1
May 2020	89	16	5
June 2020	40	5	0
July 2020	21	3	0
August 2020	25	1	0
September 2020	133	24	1
October 2020	233	35	4
November 2020	397	61	10
December 2020	466	52	19
January 2021 (before 11th)	324	71	10
January 2021 (11th onward)	785	150	59
February 2021	400	65	49
Total	**3004**	**496**	**158**

ITU, intensive therapy unit.

also collected over the same period. The proportion of hospitalised patients with COVID-19 or those admitted to ITU recruited to the trial in comparison to those who were not was used to assess recruitment success. The number of patients with COVID-19 initiated on CPAP or HFNO via or outside the trial randomisation process was also collected over the same period. Fisher's exact test was used to compare changes before and after the establishment of RSU. All analyses were done using SPSS Statistics V.27 and, in all cases, a p value of <0.05 was considered to be statistically significant.

Patient and public involvement

Patients and the public were not involved in the conception or design of the study.

RESULTS

As of 28 February 2021, a total of 158 patients were recruited into the RECOVERY-RS trial at QEHB. One hundred and eight (68.4%) of them were recruited after RSU was opened. Table 1 shows the monthly figures of patients with COVID-19 requiring hospital admission, patients with COVID-19 requiring ITU admission and patients recruited since the trial was first started at QEHB.

Before the opening of RSU, 101 patients were initiated on CPAP or HFNO with 35 (33.7%) of them being via trial randomisation. After establishment of the RSU, 73 patients were initiated on CPAP or HFNO; all of them (100%) through trial randomisation (p<0.001). The proportion of patients recruited into the RECOVERY-RS trial relative to the number of COVID-19 hospital admissions and ITU admissions were 2.8% and 17.8%, respectively, before the opening of RSU. After the RSU opening, there was a significant increase in both the proportion of recruited patients relative to the number of COVID-19 hospital admissions (9.1%; p<0.0001) and ITU admissions (50.2%, p<0.001). Figure 2 illustrates the monthly trend of this data.

DISCUSSION

In an increasingly demanding clinical setting, more efficient and effective recruitment methods for clinical trials are urgently required. This is particularly

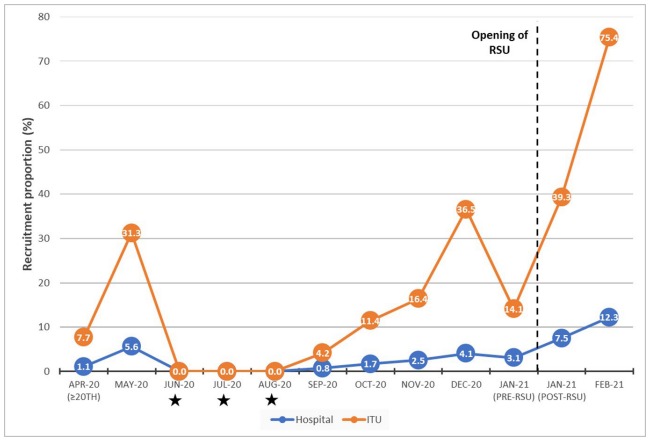

Figure 2 Monthly trend of the proportion of patients recruited into Randomised Evaluation of COVID-19 Therapy-Respiratory Support trial to the number of COVID-19 hospital admissions and ITU admissions in Queen Elizabeth Hospital Birmingham. Stars denote the months where there were ≤40 COVID-19 inpatient admissions and ≤5 ITU admissions. ITU, intensive therapy unit; RSU, respiratory support unit.

important for respiratory clinical trials as data from the National Institute of Health Research has shown that only 27 314 patients were recruited into respiratory studies[10] in comparison to 98 110 patients that were recruited into cancer studies[11] over the 2019/2020 period. Since integrating trial recruitment into the RSU CCP, recruitment to the RECOVERY-RS trial increased significantly.

One hundred and eight patients were recruited over the 49 days after the opening of RSU in comparison to 50 patients recruited over 266 days before RSU formation. By using the proportion of patients recruited relative to the number of COVID-19 hospital admissions and ITU admissions, we have also demonstrated that the increase in recruitment occurred independently of COVID-19 prevalence. Before the opening of RSU, only 33.7% of patients started on CPAP or HFNO were through trial randomisation and this increased to all patients on CPAP or HFNO after the opening of RSU.

There are several reasons why recruitment to RECOVERY-RS in QEHB has been successful. First, the pragmatic study design meant that the consent process was simplified which enabled easy and efficient incorporation of the study into the CCP. Second, there was availability of highly trained members of the multidisciplinary team (doctors, clinical nurse specialists, healthcare scientists, physiotherapists and other allied healthcare professionals) to set up and monitor patients on CPAP or HFNO throughout the day. Third, there was clear communication within the RSU consultant teams with close liaison from the intensive care team, which made escalating patients (if required) to intensive care a seamless process.

Our study has several limitations. First, this is a single-centre, observational study and therefore results from this study may not be generalisable for other healthcare centres. Another limitation is that we did not collect information regarding the number of eligible participants approached for participation and the number who declined. This would have given us a detailed look at the effect of recruitment process integration into the RSU CCP on patient willingness for trial participation. The period assessed after the establishment of RSU is relatively short compared with the period before the opening of RSU (49 days vs 266 days) and thus it is not possible to ascertain the long-term effects of this intervention on recruitment numbers. However, as there was a significant upward trend in the monthly proportion of patients recruited into the RECOVERY-RS trial as shown in figure 2, the increase in recruitment will likely be sustained for a considerable period. As COVID-19 is a novel disease, it is possible that combined with the symptom of breathlessness, this might have contributed to the willingness of patients to enrol in the study. While this may have improved recruitment to the study as a whole, there is no evidence to suggest that these factors had a greater impact pre-or post the intervention described in this study.

There have been other studies showing that integrating trial recruitment into CCPs can yield positive results in other settings as well. Shamah and Saphner demonstrated that implementing an electronic health record-integrated clinical pathway decision tool not only sped up the integration of new cancer treatments into practice but also resulted in a significant increase in clinical trial accrual.[12] The Reduction of Surgical Site Infection using a Novel Intervention (ROSSINI) trial,[13] which was a surgical trial designed and led by the West Midlands Research Collaborative, also established a successful recruitment process. Part of this success was due to recruitment being integrated into the clinical pathway through preoperative assessment clinics.[14]

CONCLUSION

A successful recruitment process into clinical trials is crucial not only to generate adequately powered results but also to minimise wastage of financial and labour costs associated with running of the trial. In respiratory medicine, where research funding is scarce, innovative new models to drive recruitment into clinical trials are required to maximise the resource available. We have demonstrated that integrating trial recruitment into care pathways within a healthcare organisation can significantly boost recruitment. However, in order to succeed, all parties involved in patient care have to agree to equipoise between trial treatment arms.

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