Intramuscular tranexamic acid for symptomatic mild traumatic brain injury in older adults: a pilot randomised, placebo-controlled trial (The CRASH-4 trial pilot phase).

The UK CRASH-4 trial collaboration (Members listed at end of paper)

ABSTRACT

Background

Mild traumatic brain injury (TBI) can cause death, disability and dementia in older adults. Timely tranexamic acid (TXA) treatment, by preventing or limiting intracranial bleeding, could reduce these risks. The CRASH-4 trial will assess the effects of early intramuscular TXA in older adults with mild TBI. To test the trial procedures and the acceptability of the intervention, we conducted a pilot phase.

Methods

We recruited patients aged 50 years or older if they had a history or signs (laceration, bruise, swelling or pain in head or face) of a head injury; a GCS ≥ 13; any impairment of consciousness and were within 3 hours of the injury. We enrolled patients at the scene of the injury or in the ambulance. We also enrolled patients who presented directly to the emergency department. We randomly allocated patients to receive an intramuscular injection of 500 mg tranexamic acid or matching placebo. We gave one 5mL injection (100mg/ml TXA or placebo) or two 2.5mL injections depending on muscle mass. The objectives of the pilot were (1) to test all trial procedures, including the willingness of paramedics and emergency physicians to recruit patients and the willingness of patients to be enrolled, (2) to determine the rate of recruitment (number of patients per site per month), (3) to assess the acceptability of the intramuscular injection and (4) to determine event rates and rates of follow up.

Results

We recruited 493 patients between April 2021 and July 2022. Their mean age was 73 years (SD=12 years) and 246 (50%) of patients were female. The mean time from injury to randomization was 2.4 hours (SD=0.7 hours). The average recruitment rate was 1.7 patients per site per month. A single 5mL injection was received by 62% of patients and 38% of patients received two 2.5mL injections. An injection site reaction was reported in 4 patients, all of whom had bruising at the injection site (0.8%). There were 27 serious adverse events reported but none were suspected to be related to the trial treatment. Of the 483 randomised participants with outcome data, 54% were discharged from the emergency department within 24 h of their injury (n=261). Of the 220 patients that were admitted to hospital, 41% were admitted due to their head injury, 45% were admitted for another injury or medical condition, 4% were admitted while awaiting transfer to the community and 10% were admitted for other reasons. The average duration of hospital admission was 0.4 days (IQR=0.2-2.2). The average duration of admission was 4.6 days (IQR=2.1-10.7) for patients with intracranial haemorrhage compared to 0.4 days (IQR=0.2-1.8) for patients who did not. 43 patients had intracranial bleeding (9%), 3 had neurosurgery (0.6%) and 7 patients died (1.5%).

Discussion

The intramuscular injection (TXA or placebo) was well tolerated by older adults with mild TBI. Based on the observed recruitment and outcome event rates, a large trial of the efficacy and safety of early intramuscular tranexamic acid for older adults with mild traumatic brain injury appears feasible.

Trial registration: The trial is registered at ClinicalTrials.gov: NCT04521881 and EudraCT number: 2020-003391-40.

Keywords: Antifibrinolytic; clinical trial; tranexamic acid; traumatic brain injury; intracranial bleeding.

BACKGROUND

Over one million people attend emergency departments in the UK every year after a mild traumatic brain injury (TBI). Although a mild TBI rarely has serious health consequences in young people, in older adults it can cause death, disability and dementia, particularly in those with intracranial bleeding. [1] Even mild TBI without loss of consciousness doubles dementia risk. [2,3,4] Because the UK population is ageing, the burden of disability and dementia due to TBI will increase.

In the early hours after mild TBI, intracranial bleeding is the main threat to life and health. Due to changes in brain anatomy with increasing age and the greater use of anticoagulant and antiplatelet drugs, intracranial bleeding is more common in older adults. [5,6,7] NICE guidelines recommend a CT scan within 8 hours of injury in all people over 65 with any alteration of consciousness. [8] However, older adults can have intracranial bleeding despite being fully conscious. Cerebral atrophy allows more blood to accumulate before the intracranial pressure rises and the GCS falls. As a result, CT scanning and neurosurgery are often delayed. Even small bleeds that do not need evacuation increase disability and dementia as the inflammatory response to blood in brain tissue can lead to brain cell death. [9]

The CRASH-3 trial results raise the hope that early TXA treatment of older adults with mild TBI could prevent death, disability and dementia and reduce the need for hospital admission. The CRASH-3 trial recruited 9,202 patients within 3 hours of injury if they had moderate or severe TBI (GCS≤12) or mild TBI with intracranial bleeding on CT scan (complicated mild TBI). [10] TXA reduced head injury deaths. The benefit was greatest in complicated mild TBI, probably because intracranial bleeding is the main cause of death after mild TBI, and because these patients have less intracranial bleeding at baseline, there is more potential to prevent bleeding. [11] Patients with severe TBI often have extensive intracranial bleeding at baseline or other life-threatening intracranial pathologies that are not affected by TXA. In complicated mild TBI, there was a strong time to treatment interaction. Every 20 minutes treatment delay reduced the benefit by 10%. There was no increase in thrombotic events or other serious side effects with TXA. Because older adults have a high risk of intracranial bleeding and TXA has an excellent safety profile, the balance of benefits and risks from early TXA treatment of mild TBI prior to CT scanning should be favourable. If TXA improves outcomes by preventing intracranial bleeding, we should not wait until bleeding is present.

To reduce delay, patients should be treated by paramedics at the scene. In major trauma patients, median time to treatment is 51 minutes when TXA is given pre-hospital and 112 minutes when TXA is given in-hospital. [12] Recent research has shown that TXA is well tolerated and rapidly absorbed after intramuscular (IM) injection. [13] IM treatment simplifies pre-hospital TXA use. IV TXA must be given by slow injection over 10 minutes. Qualitative research with UK paramedics shows that this slow intravenous injection is a barrier to pre-hospital use. [14] However, IM TXA achieves therapeutic levels within the time it takes to complete the IV injection (10 mins) and does not require IV cannula insertion. A single pre-hospital IM TXA injection might be seen as a 'vaccine' to prevent intracranial bleeding. The CRASH-4 trial will determine whether early IM TXA treatment of older adults with mild head injury can prevent death, disability and dementia and increase early return to independent living at home.

We report the pilot phase of the CRASH-4 trial. We aimed to enrol about 500 older adults with mild TBI to test all the trial procedures, including the willingness of paramedics and emergency physicians to randomise patients, the willingness of patients to be enrolled, the acceptability of the intramuscular injection and the outcome event and follow up rates.

METHODS

We developed the trial protocol with input from experts in emergency care, neurosurgery, care of the elderly and prehospital care, as well as trialists, statisticians and a patient panel. The patient panel advised on patient documents and recruitment and retention methods. They helped draft the protocol summary, the information sheets and consent forms. They advised on outcome measure and the choice of primary outcome. Many trial procedures were specifically designed to respond to the COVID-19 pandemic. To test all trial procedures, we conducted a pilot phase. We tested (1) remote site set-up and investigator training (2) the use of an electronic site file that can be accessed from anywhere by paramedics and emergency care staff without using paper documents that might transmit infection (3) the ability of paramedics to screen, consent, collect baseline data, randomise and administer the trial drug to eligible patients (4) the use of electronic consent forms (5) follow up of patients enrolled pre-hospital and taken to non-participating hospitals and (6) compliance with IMP regulatory requirements by paramedics.

Study design and participants: We conducted a randomised placebo-controlled trial of intramuscular tranexamic acid in older adults (age 50 or older) with symptomatic mild traumatic brain injury. Patients were enrolled at the scene of the injury or in the ambulance, or after presenting to a hospital emergency department. Patients were eligible if they had a history or signs (laceration, bruise, swelling or pain in head or face) of a head injury; a GCS ≥ 13; any impairment of consciousness (loss of consciousness, amnesia, or confusion, nausea or vomiting) and were within 3 hours of injury. Patients were not included if: (1) time since injury could not be estimated e.g. found on floor after an unwitnessed fall, (2) patient lived in a nursing home, hospital or prison, (3) the patient would not be conveyed to hospital (pre-hospital recruitment).

Because of the nature of their injury, some patients with mild TBI are unable to provide written informed consent. We developed a consent procedure in line with the UK Clinical Trials Regulations. The consent method used depends on the capacity of the patient and whether a friend or relative is present (and their capacity). There are several options: written consent from the patient, relative or professional representative, assent from the patient or relative, or defer consent. If consent or assent could not be obtained, consent was deferred and the patient was enrolled without prior consent. In these cases, the hospital team obtained consent once the emergency was over. If patients did not regain capacity, consent was sought from a relative, friend or professional representative. Patients or their representatives were able to withdraw consent at any time without giving a reason. We adhered to the requirements of the local and national ethics committees. The protocol was approved by South Central - Berkshire Research Ethics Committee, Health Research Authority (HRA) and Medicines and Healthcare Regulatory Agency (MHRA).

Randomisation and masking: We used block randomisation to increase the chance that each arm has a similar number of patients. An information technology (IT) specialist who was not involved in the trial prepared the randomisation list using Stata's random-number generation and the seed function. The randomisation codes were given to the clinical trial supply company by the IT Specialist in a secure way so that the blinded treatment packs could be prepared. Patients were randomised by selecting and administering the dose from a uniquely numbered treatment pack from a box of blinded packs (identical apart from the pack number) (Figure 1). The point of randomisation was administration of the first injection. Treatment and placebo ampoules were identical in appearance. Patients, caregivers, and all trial staff were masked to treatment allocation.

IMP pack design: We worked with paramedics to design the IMP treatment pack. There is little space within an ambulance and the pack must meet infection control requirements. Small, wipeable PVC pouches were manufactured (Figure 1). Each had a carabiner to attach the pouch to the paramedic's belt or bag. The packs are orange to avoid confusion with standard kit (neon yellow and green). To avoid confusion between clinical use TXA and the IMP, the word 'tranexamic acid' is not shown on the outside of the pack. The pouch contains an orange patient wristband and source data labels for handover at hospital. (Figure 2). The wristband identifies CRASH-4 trial patients reducing the risk of second randomisation in hospital. The labels allow documentation of IMP administration in the medical record. Ampoules are protected with foam padding to avoid breakage (Figure 1). Administration instructions are on the pack lid for quick reference in an emergency. The IMP pack design complies with EU labelling rules (Annex 13).

Health technologies being assessed: The intervention was a 500mg IM injection of tranexamic acid. TXA reduces bleeding by inhibiting fibrinolysis. Bleeding occurs soon after injury and so the therapeutic objective is rapid inhibition of fibrinolysis. Our pharmacodynamic studies shows that a plasma TXA concentration between 5 and 10 mg/L substantially inhibits fibrinolysis.[15] Our pharmacokinetic studies show that after a 500mg TXA IM injection, a concentration of 5 mg/L is achieved within 10 mins and a TXA concentration of 10 mg/L is achieved within 20 mins.[16] Due to the rapid absorption of TXA from muscle and the greater ease of IM use, therapeutic levels should be achieved faster with IM injection than with IV injection (needs cannula insertion and slow injection). Our PK modelling showed that a 500 mg dose is safe in older adults even with reduced renal function. The intervention of 500mg TXA was given as a single 5mL IM injection of 100mg/ml or two x 2.5mL IM injections depending on muscle mass, as soon as possible after injury but no later than 3 hours. The injections were given into the arm (deltoid), thigh (rectus femoris or vastus lateralis) or buttocks (gluteal muscles). The comparator was a matching (0.9% saline) placebo. The only difference between usual care and the CRASH-4 trial protocol was that patients received an IM injection of TXA or placebo. There were no other differences in patient management and no extra tests.

Measurement of outcomes: The primary outcome was discharge from the emergency department within 24 hours of arrival. Patients were assessed for discharge by a healthcare professional. If a patient was discharged from the emergency department without hospital admission, the patient was considered to have a good outcome. Return to independent living at home is highly valued by older people and a good indicator of short-term recovery. It is also an important issue for health and social services with major cost implications. Secondary outcomes were presence and type of intracranial bleeding on CT scan, death, disability, ability to self-care, neurosurgery, intensive care admission, vascular occlusive events (pulmonary embolism, myocardial infarction, deep vein thrombosis and stroke), seizures, injection site reaction and pneumonia. All-cause dementia or death will be determined 12 months after injury. Dementia will be identified through linkage to routinely collected health-care data from NHS Digital / NWIS. Recent systematic reviews showed that the accuracy of dementia diagnosis in these routinely collected datasets is high. [17] Dementia is defined according to ICD-10 codes. Studies of the accuracy of dementia diagnoses in HES dataset (using data from a large mental health care database as gold standard) show that the specificity of dementia recording is high (92%). Although sensitivity was 78%, provided there are few false positives (high specificity), estimates of the relative risk are unbiased even when the sensitivity is imperfect.

Pilot phase objectives: The objectives of the pilot were (1) to test all trial procedures, including the willingness of paramedics and emergency physicians to recruit patients and the willingness of patients to be enrolled, (2) to determine the rate of recruitment (number of patients per site per month), (3)

to assess the acceptability of the intramuscular injection and (4) to determine event rates and follow up. For the estimation of the recruitment rate, a site is defined as a hospital or an ambulance station.

Sample size: Study size depends on the event rate (same day discharge) and the magnitude of the treatment benefit. When planning this trial, we predicted the event rate from the literature (35%) and calculated that we would need about 10,000 patients to detect a 15% increase in same day discharge. However, we recognised that the study size may change based on information from the pilot. The pilot phase aimed to recruit about 500 patients. A pilot phase of this size should provide a robust test of the trial procedures and provide a suitably precise estimate of the expected event rates.

Role of the funding source: The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Trial Procedures: Details of the procedural innovations developed during the pilot phase are shown in the Appendix. Many of these were in response to the COVID-19 pandemic. The trial procedures were fully tested.

Paramedic training and recruitment: A total of 680 clinicians (280 paramedics) have completed the online training. We recruited 493 patients between April 2021 and July 2022 (Figure 3). As of 27 July, 35 sites were recruiting (20 hospitals and 15 ambulance stations from 2 ambulance trusts). A total of 73 hospital research staff and 78 paramedics recruited one or more patients. For the last three months, average recruitment was 1.7 patients per site per month.

Consent procedure used: To reduce the impact of patient recruitment on paramedic workload we used an electronic consent system. The patient provided consent in 57% of cases, a relative in 11% of cases and a professional legal representative in 8% of cases. Consent was deferred in 23% cases. The electronic consent system was used for 156 randomised participants.

Baseline characteristics: Baseline patient characteristics are shown in Table 1. The mean age was 73 years and 50% were female. Mean time from injury to randomisation was 2.4 hours (SD=0.7 h). In patients recruited pre-hospital, mean time from injury to randomisation was 2.0 hours (SD=0.7 h). In those recruited by the emergency department, mean time from injury to randomisation was 2.7 hours (SD=0.5 h).

Acceptability of intramuscular injection: All patients received the full dose of the trial treatment (tranexamic acid or saline placebo). 62% of patients received a single 5mL injection and 38% received two 2.5mL injections (a divided dose). An injection site reaction was reported in 4 patients, all of whom experienced bruising at the injection site. There were 27 serious adverse events reported. None of these were suspected to be related to the trial treatment.

Event rates and follow up: Of the 493 randomised participants, 483 were followed up (98%). Of those with outcome data, 54% were discharged from the emergency department on the day of the injury (n=261). Of the 220 patients that were admitted to hospital, 41% were admitted due to their head injury, 45% were admitted for another injury or medical condition, 4% were admitted while awaiting transfer to the community and 10% were admitted for other reasons. The average duration of hospital admission was 0.4 days (IQR=0.2-2.2). There was CT evidence of intracranial haemorrhage in 43 (9%) patients. Average duration of admission was 4.6 days (IQR=2.1-10.7) in patients with intracranial haemorrhage and 0.4 days (IQR=0.2-1.8) in those without. Table 2 shows the outcome data.

DISCUSSION

The pilot phase tested all study procedures, provided estimates of the recruitment and event rates and confirmed the acceptability of the intramuscular injection. The study procedures worked well. We made several protocol amendments during the pilot phase. We reduced the age limit for recruitment from 70 to 50 years. An early economic decision model comparing usual care for mild TBI with and without tranexamic acid for adults aged 70 and over, showed that the expected value of the information provided by the CRASH-4 trial is high (£22 million).[18] However, the analysis also showed that expanding recruitment to age 50 would more than double the expected value of the information provided, due to the larger population that would benefit from the treatment decision. This change also increased recruitment and during the last three months of the pilot, we recruited nearly 2 patients per site per month. We initially excluded patients 'known to have a diagnosis of dementia.' This exclusion was removed after feedback from paramedics showed that it is difficult to determine in the emergency situation without access to medical records. Furthermore, because dementia is a strong risk factors for falls, the Trial Steering Committee pointed out that it would be important to evaluate the effect of TXA in people with dementia. We added the 'clinical frailty score' to baseline data collection because it is highly prognostic and care of the elderly experts told us that it will soon be recorded for all patients. Because patients are sometimes discharged at night when research staff are unavailable, the protocol was amended to allow disability data collection by telephone interview.

We recruited approximately 2 patients per site per month. A site is defined as a hospital or an ambulance station. At the time of writing, 35 sites were recruiting (20 hospitals and 15 ambulance stations across two Ambulance Services) and we expect 40 sites by Feb 23. In the main phase, we will start another 10 hospitals and 35 ambulance stations. We already have expressions of interest from 9 hospitals and 6 Ambulance Services. Based on these data, we are confident that we can recruit a total of 5,000 patients over a 30-month recruitment period (Figure 4). Patient follow up was almost complete.

When planning the CRASH-4 trial, we predicted the event rate from the literature (35%) and calculated that we would need about 10,000 patients to detect a 15% increase in same day discharge. However, after recruiting nearly 500 patients in the pilot phase, we find that the event rate is higher (50%). Furthermore, our economic decision modelling shows that because TXA is cheap and easy to use, it would be highly cost-effective for the NHS with only a very modest treatment benefit. [18] Based on these data, assuming pre-hospital IM TXA increases same day discharge from UK hospitals from 50% to 55% (RR=1.10) a study of 5,000 patients would have over 90% power at the 0.05 significance level. We will amend the protocol to reduce the sample size (and any other changes requested by NIHR).

The intramuscular injection was well tolerated with only a few minor local reactions. The average time from injury to treatment was 2.4 hours. The beneficial effect of tranexamic acid in acute traumatic bleeding varies with time to treatment with early treatment being most effective. Although data from the CRASH-3 trial show that we might expect a significant treatment benefit up to 3 hours, we will continue to emphasise the importance of timely treatment. Ambulance service innovations to reduce time to treatment include the use of research cars that are dispatched to potentially eligible patients. https://www.youtube.com/watch?v=zaR3eiQ4Jlc&t=2s

Recent research has strengthened the case for a trial of intramuscular (IM) tranexamic acid in older adults with mild traumatic brain injury. Our pharmacokinetic studies have confirmed that tranexamic acid is well tolerated and rapidly absorbed after IM injection, reaching a therapeutic concentration within minutes of injection. [19] By reducing time to treatment, the use of the IM route should increase the size of any treatment benefit. In the UK, less severely injured patients are much less likely to receive tranexamic acid. However, our individual patient data meta-analysis shows that early

treatment improves outcome to a similar extent in severely and non-severely injured patients. [20,21] UK ambulance guidelines on tranexamic acid for traumatic brain injury restricts use to patients with moderate and severe brain injury. The CRASH-4 trial will be the first trial of TXA in patients with mild TBI and there is good reason to expect a treatment benefit. Analyses of UK trauma audit data show that TXA reduces mortality to a similar extent in women and men, but women are much less likely to be treated with TXA. [22] The sex difference in the receipt of TXA increased with increasing age. Because older women are more often injured in falls at home and take longer to reach hospital, it is often too late to treat them with TXA. By treating older TBI patients in their homes or on hospital arrival, without waiting for a scan, we should maximise patient benefit and reduce inequalities. It is reassuring that 50% of the patients included in the pilot phase were women.

The CRASH-4 trial will determine whether early TXA treatment of older adults with mild head injury can prevent death, disability and dementia and avoid the need for hospital admission. Hundreds of thousands of patients attend emergency departments after mild traumatic brain injury. The main threat is intracranial bleeding. Timely TXA treatment could prevent intracranial bleeding but most patients are seen too late to benefit. In general, mild TBI patients attend emergency departments where they are admitted, observed and discharged but not treated. This worsens hospital overcrowding with marginal patient benefit. The information from this trial could improve treatment strategies. Rather than being admitted but not treated, mild TBI patients could be treated and (on many occasions) not admitted. In this trial, we take the treatment to the patient. An early IM injection tranexamic acid at the scene could reduce intracranial bleeding and the need for hospital admission.

Authors' contributions: DB, DP, EA, CG, LC, AB, RM, MM, AT, MB, HSS and IR drafted the paper. AB conducted the analyses. All authors critically revised the paper and approved the final version.

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Availability of data and materials: When completed the data from the CRASH-4 trial will be made available from The Free Bank of Injury and Emergency Research Data (freeBIRD) website, a data sharing portal.

Ethics approval: Ethics approval for the CRASH-4 trial was obtained from the South Central - Berkshire Research Ethics Committee. REC reference:20/SC/0372.

Competing interests: The authors declare that they have no competing interests.

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Appendix: Procedural innovations implemented for the pilot phase.

(1) Remote set-up and investigator training: Due to the COVID-19 pandemic, site set up and training was remote via videoconferences with the Clinical Trials Unit and on-line self-learning with videos, animation, presentations and documents hosted on REDCap. Paramedic training involved 11 short videos covering the trial procedures and GCP. Learning was tested in a quiz with a 100% score to pass. Once trained, the paramedic was included on the electronic delegation log.

(2) Electronic site file: The site file must be accessible wherever paramedics work and avoid the need for paper documents that could transmit infection. We created an electronic site file using REDCap. This was accessed by all users with no issue, and was easy to maintain in line with GCP.

(3) Pre-hospital recruitment: Electronic systems (trial database, eConsent system) were developed to document all trial procedures (screening, consent, randomisation, data collection). The London Ambulance Service created a CRASH-4 trial application (an app) that was embedded into the electronic patient record. The trial procedures were successfully documented using electronic devices issued to paramedics as part of their standard role for 221 patients. There were 4 screening failures when patients consented but were not randomised. To increase paramedic recruitment the South-Central Ambulance Service (SCAS) have established a system of research cars (ambulance cars staffed by research paramedics) that attend potentially eligible patients and recruit them if appropriate. They then hand the patient over to a regular ambulance for transport. The research cars are supported by the Wessex and the Thames Valley & South Midlands Clinical Research Networks. Further details are available here: https://www.youtube.com/watch?v=zaR3eiQ4Jlc&t=2s**.** SCAS recruited their 1st patient in June 21. Their total recruitment by the end of September 21 was 5 patients. They implemented the research car initiative in October 21, and by the end of November 21 had recruited 20 patients. With 129 randomised patients, SCAS is the highest recruiting ambulance service. Based on their experience, the North East Ambulance Service has also introduced a research car, supported by their Clinical Research Network.

(4) Electronic consent: The eConsent system is accessible on tablets/iPads held by paramedics on ambulances and is available in emergency departments. The London Ambulance Service developed its own eConsent system, integrated into their electronic medical record. It complies with GDPR and all regulatory requirements. eConsent has been used successfully by paramedics and emergency staff.

(5) Patient follow up: Data Sharing Agreements and letters of access between the ambulance service and non-participating sites allowed pre-hospital recruitment and follow up via remote access to the hospital patient records. Trial paramedics inform research paramedics about patient recruitment, and the trial database sends an automated email to the research paramedic alerting them of a recruit. The research paramedic checks the patient's hospital records daily for adverse events, and completes the outcome form remotely when due. The research paramedic calls the patient for the disability data, and obtains follow up consent where needed. Readmissions to hospital are also checked via remote record access up to day 28. The ambulance service has a 98% follow up rate with no missing disability data.

(6) IMP management: An IMP risk assessment is completed for each site to ensure proper handling including receipt, transfer, storage, restricted access, temperature monitoring and accountability and appropriate oversight by a pharmacist. To ensure IMP accountability by paramedics at the start and end of their shift, they complete a drug collection and return log which is kept with the IMP at site. One ambulance service added the CRASH-4 trial drug to their electronic drug accountability system to bring it in line with routine practice, reducing the workload for paramedics and pharmacists. There was one breach of IMP management at a site. The corrective and preventative action included, where appropriate to do so at a site, a label being added, overseen by the pharmacy team, to the CRASH-4 IMP packs (on the outside of the plastic pouch) with details of where it should be returned if lost.

Figure 1: CRASH-4 IMP treatment box and IMP pouches.

Figure 2: CRASH-4 orange wristband and data labels for handover at hospital and on-going care.

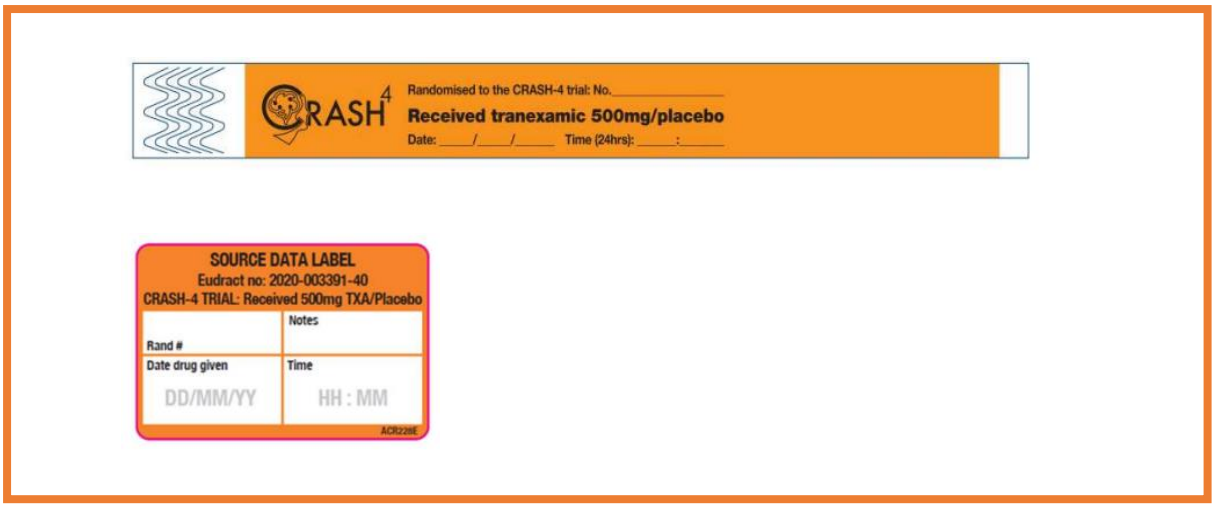
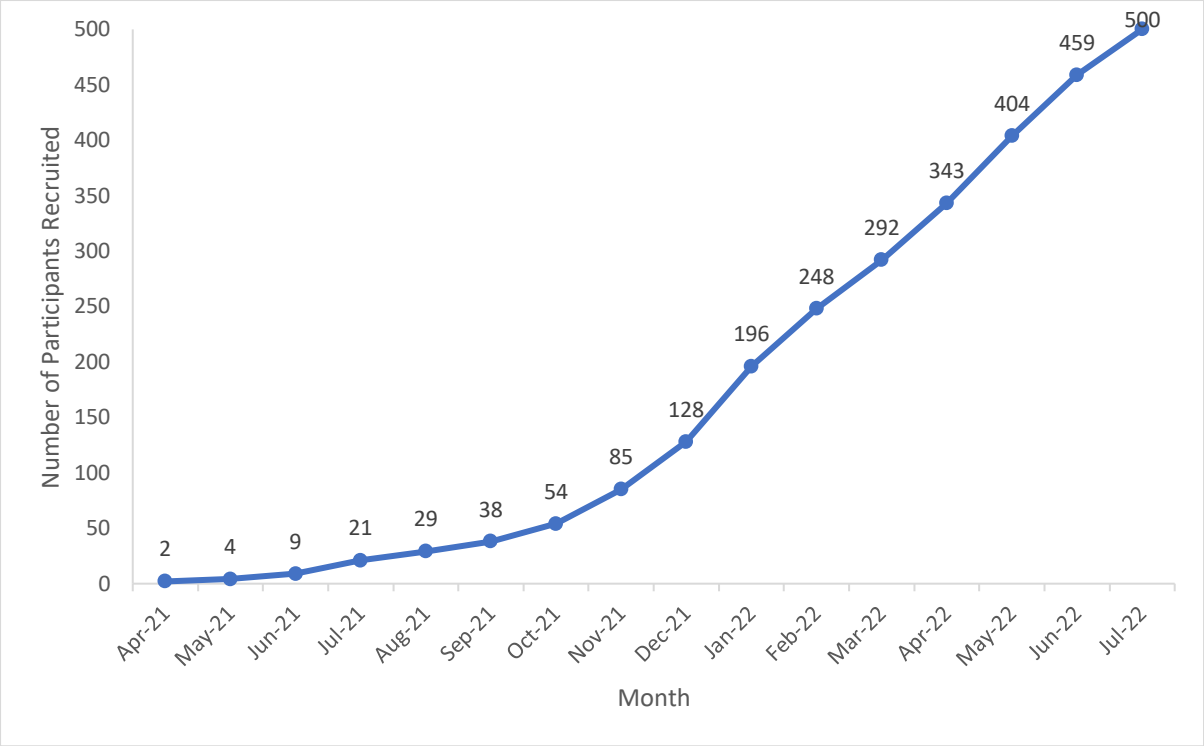


Figure 3: Current CRASH-4 Recruitment April 2021 – July 2022



Current recruitment rate per site per month = 1.7. Projected recruitment (Figure 4 below) is based on this.

Figure 4: Projected CRASH-4 Recruitment February 2023 – August 2025

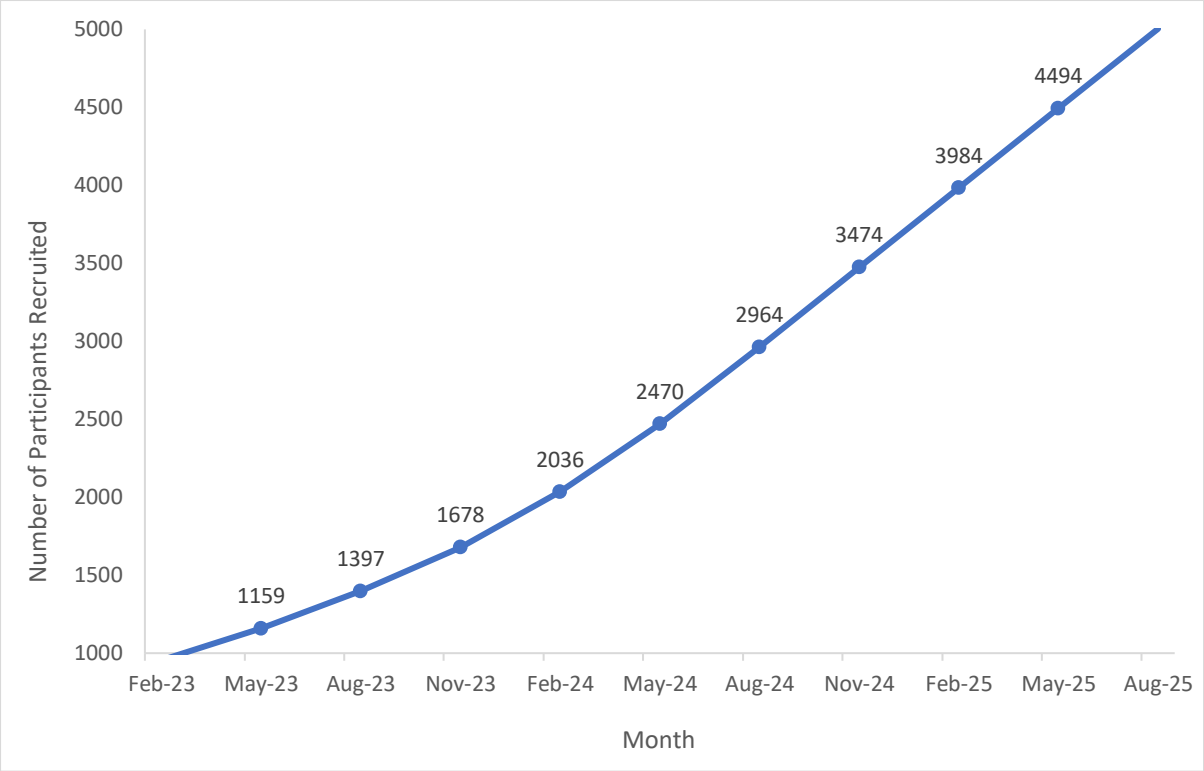


Table 1. Baseline data - all patients randomised

Percentages are of group total unless specified		**All patients**	(N=493)
Patients randomized as of 27th July 2022		N	(%)
Age (years)	Mean age (SD)	73.3	(12.4)
	50-59	89	(18.1)
	60-69	97	(19.7)
	70-79	121	(24.5)
	80-89	144	(29.2)
	≥90	42	(8.5)
Sex	Male	246	(49.9)
	Female	247	(50.1)
Brain injury symptoms since head injury	Loss of consciousness	228	(46.2)
	Amnesia	236	(47.9)
	Confusion/drowsy	205	(41.6)
	Nausea	151	(30.6)
	Vomiting	63	(12.8)
Estimated time since injury (hours)	≤1	54	(11)
	>1-2	211	(42.8)
	>2-3	228	(46.2)
Pupil reaction	Both react	478	(97)
	One reacts	7	(1.4)
	Unable to assess	8	(1.6)
GCS Eye opening	Spontaneous: 4	483	(98.0)
	To sound: 3	10	(2.0)
	To pain: 2	0	(0)
GCS Verbal response	Orientated: 5	380	(77.1)
	Confused speech: 4	111	(22.5)
	Words: 3	2	(0.4)
GCS Motor response	Obeys commands: 6	490	(99.4)
	Localizing: 5	3	(0.6)
	Normal flexion: 4	0	(0)
GCS Score	15	377	(76.5)
	14	104	(21.1)
	13	12	(2.4)
Respiratory rate	>25	9	(1.8)
	20-24	95	(19.3)
	15-19	366	(74.2)
	<15	22	(4.5)
Heart rate	>79	233	(47.3)
	70-79	113	(22.9)
	60-69	109	(22.1)
	<60	37	(7.5)
Systolic BP (mmHg)	>139	286	(58)
	130–139	74	(15)
	120–129	58	(11.8)
	<120	74	(15)
Diastolic BP (mmHg)	>89	138	(28)
	80–89	147	(29.8)
	75–79	68	(13.8)
	<75	139	(28.2)

Currently taking anticoagulants	Yes	101	(20.5)
	No	389	(78.9)
	Don’t know	3	(0.6)
Currently taking antiplatelets	Yes	74	(15)
	No	417	(84.6)
	Don’t know	2	(0.4)
Clinical frailty score	≥5	123	(24.9)
	3-4	115	(23.3)
	1-2	137	(27.8)

Table 2. Patient Outcomes – all patients with outcome data available

Percentages are of total number of patients with outcome data	**All patients**	**(N=493)**
Patients followed up as of 27th July 2022	**n**	**(%)**
Discharge from the ED in 24h	263	(54.5)
Admitted to hospital for head injury	91	(18.8)
Average number of days in hospital (median, IQR)	0.4	(0.2-2.2)
Admitted to intensive care	5	(1.0)
Average number of days in intensive care (mean, SD)	0.1	(0.8)
Intracranial bleeding present on CT scan	43	(8.9)
Epidural only	2	(0.4)
Subdural only	16	(3.3)
Subarachnoid only	11	(2.3)
Parenchymal only	1	(0.2)
Intraventricular only	13	(2.7)
Multiple	2	(0.4)
Neurosurgical operation	3	(0.6)
Death within 28 days (all-cause)	7	(1.4)
Cause of death		
Head injury	1	(0.2)
Multi organ failure	2	(0.4)
Myocardial infarction	1	(0.2)
Pneumonia	1	(0.2)
Other	2	(0.4)
Adverse events		
Deep vein thrombosis	1	(0.2)
Pulmonary embolism	0	(0)
Myocardial infarction	3	(0.6)
Stroke	1	(0.2)
Seizure	1	(0.2)
Pneumonia	4	(0.8)
Global selfcare assessment. As a result of the head injury:		
Patient is completely dependent on care from others	3	(0.6)
Patient is extremely dependent on care from others	13	(2.7)
Patient is partly dependent on care from others	27	(5.6)
Patient has only a limited dependence on care from others	429	(88.8)
Patient is fully independent	3	(0.6)
Disability assessment (Barthel Index)		
Total dependence or death	9	(1.9)
Severe dependence	33	(6.8)
Moderate dependence	32	(6.6)
Slight dependence	408	(84.5)

CRASH-4 Collaborators

CTU

Ian Roberts, Haleema Shakur-Still, Amy Brenner, Danielle Beaumont, Emma Austin, Catherine Gilliam, Laura Carrington, Danielle Prowse, Andrew Thayne, Mbwana Mohammed, Amber Geer, Raoul Mansukhani, Myriam Benyahia

DATA MONITORING COMMITTEE
Carrol Gamble, Elaine Cole, Tim Nutbeam

TRIAL STEERING COMMITTEE
Jay Banerjee, Sara Dowling, Pam Foley, Gavin Perkins, Natalie Teich, Alex Ulrich

SITES

Addenbrooke's Hospital
Rishi Rallan, Adrian Boyle, Justin Ang, William Pritchard, Richard Kendall, Catherine Hayhurst, Lisa Ramage, Lee Soomaroo, Sajjad Ahmed, Andrew Scott-Donkin, Susie Hardwick, Kerry Meynell

Chelsea and Westminster Hospital
Shweta Gidwani, Matthew Spriggs, Philippa Nicklin, Julia Burkert, Arjun Lakhani, Fiqry Fadhlillah, Tulika Rajen, Alexandra Schoolmeesters

Croydon Hospital
Kathryn Channing, Jen Robbins, Ruth Watson, Roshan D'Souza, Pramod Venkapayya, Sakthi Muthalraju, Siobhan Dutton, Harsha Kodakadath, Runal Shah, Oliver Spencer, Salwa Adam, Elena Baraldi, Susan Lamey, Charlie Morvan, Helen Gleave

Dorset County Hospital
Tamsin Ribbons, Spencer Cheung, Rachel Wharton, Joanne Mahy, Kess Akowheri, James Rees, Ashleigh Cave, Sarah Williams

Epsom Hospital
Rebecca Macfarlane, Lisa Evans, Marco Machado, Sumaya Huque, Nadeem Ishtiaq, Suzanne Goddard, Ansareen Untoo, Shilpa Gajjar, Anna Laurenson, Amir Hassan, Nilan Subra, Tim Oreo, Robert Tan, Richard Opom, Grace Blows, Manuel Rebolledo, Amy Matthews

Good Hope Hospital
Sarafina Vatharkar, Susan Dorrian, Raj Jha, Aimee Wright, Clarice Howie, Victoria Siddons, Sikander Majid, Clare O'Carroll, Ruth Beveridge, Mohammad Saim, Heather Willis, Rele Ologunde, Sally Lynch, Alexandra Clement

Great Western Hospital
Stephen Haig, Samantha Burke, Tim Slade, Nicola Clark, Laura McCafferty

Kettering General Hospital
Mohammed Elwan, Andrei Ionel, Sareesh Bandapaati, Hannah Britton, Parizade Raymode, Julie Sebastian, John Obiakor

King's College Hospital

Fleur Cantle, Matthew Edwards, Phil Hopkins, Firas Sa'adedin, Cara Jennings, Elidh Gilchrist, Malcolm Tunnicliff, Frances Arnold, Clare Donegan, Annabel Driscoll, Joshua Clough, Emer Sutherland, Panagiotis Kyrtatos, Aileen Balagot, Duncan Bew, Hannah Cotton, Simone Waitt, John Smith, Emma Clarey, Maria Depante, Kevin O'Reilly

Leeds General Infirmary
Clare Thompson, Kiran Chana, Sophie Griffin, Catherine Holmes, Sally Price, Laura Milnes, Tadas Mazeika, Shahzadi Zeb, Mayada Elsheikh, Natasha Calder-Smith, Gary Lamont

Leicester Royal Infirmary
Scott Knapp, Tracy Harris, Adele Holland, Harriet Gough-Jennings, Vivek Pillai, Benjamin Feist

London Ambulance Service (LAS)
Fenella Wrigley, Adam Mellett-Smith, Rachael Fothergill, Justin Kearney, Clara Bannister

LAS ambulance stations: Wimbledon, Putney, Waterloo, Deptford, Oval, Brixton, Croydon, South Croydon, St Helier: Abbey Woolsey, Abigail Blundell, Adam Stephenson, Alex Kellermann, Alex Kruger, Alexander Stroszynski, Alice Usborne, Amy Cotter, Andrew Fitt, Andrew Sutton, Ania Geaghan, Benjamin Cottrell-Dormer, Benjamin Hardy, Benjamin Stapleton, Benjamin Vickars, Brittany Mathison, Bronwyn Inns, Calum Sinclair, Christopher Chapman, Claire Brunavs, Clare Davis , Clare Wright, Collene Esteban, Craig Francis, Curtis Rutter, Daniel Dollin, Daniel Gullis, Daniel Randall, Daniel Rejniak, Daniel Sarabia-Amparan, Daniele Contessa, Darryn Nuthall, David Long, Donald Macrae, Donna West, Eleanor Welham, Ellen Cockburn-Heeley , Francis Biggin, Gabriela Sobczak, Gabriele Cucinella, Gareth Cross, Gareth Woodley, George King, George Laughton, Georgia Lorente, Hannah Baffa, Harriet Walton, Heide Martin, Heidi Sullivan, Helen Chiverton, Jack Davies, Jack Holland , James Colless, James O'Grady, Jamie King, Jane Battle , Jemma Gilder, Juan Bedoya, Katherine Sandys, Kathryn Payn, Katie Straker, Kelly Tolman, Kevin Austin, Konstantinos Papakonstantinou, Laura Jolley, Laura Taylor, Lauren Kernich, Leanne Brice, Leanne Wilcock, Liam Herneman, Lindsey Davis, Lisa Farrell, Louise Forrest, Lucy Fraser , Martin Clayton, Matthew Cooke, Matthew Galvin, Matthew Searles, Michael Hannah, Michael Parsons, Michael Swan , Mollie Lewis, Natalie Allen-Block, Natalie Cole, Natalie Williams, Natasha Pierini, Nicholas Tippett, Nigel Lee , Olivia Grez Haniewicz, Patrick wright, Philip Guthrie, Philip Watson, Rachel Taylor, Rae Childs, Raymond Batchelor, Rebecca Elliot, Rebecca Kempton, Reece Evans, Ross Catton, Rowena Rickson, Sadie Ward , Samuel Nixon, Sarah Cliffe, Sarah Levinson, Scott McCall, Selina Parris, Shona Lambe, Sonal Shah, Stephanie Smith, Stephen Young, Susan Palmer, Teresa Johnson, Trina Conroy, William Dunkerley, William Landman , William Wilson, Zachariah Joseph-Hopcraft

Manchester Royal Infirmary
Simon Carley, Richard Body, Rose Jama, Dominique Jones, Deborah Paripoorani, Emily Weaver-Holding, Hayley Riding, Jonathan Logan, Ann Booth, Atiyya Waka, Charlotte Taylor, Melanie Barker, Peter Hulme

Milton Keynes Hospital
Divyansh Gulati, Vani Muthusami, Soma Hadju, Lee How, Ayesha Dias, Mohammad Riaz Khan, Sweta Patel, Shindo Francis, Ankit Mishra, Mukul Shah, Muhammad Qureshi, Annie Rose, Muni Akande

Musgrove Park Hospital
Tony Kehoe, Wayne Battishill, Emma Machin, James Gagg, Charmaine Shovelton, Rebecca Purnell, Gemma Chilcott

Northumbria Specialist Emergency Care Hospital

Mark Harrison, Claire Garland, Lauren Nellins, Rebecca Emmonds, Dilraj Bhullar, Gemma McCafferty, Hannah Peggie, Jessica Reynolds, Tracy Smith, David Ng, Anna Wilkinson, Lisa Gallagher, David Hewitson, Gail Waddell, Hayley Mckie, Rachel Joseph

Queen Elizabeth Hospital, Birmingham
Sarafina Vatharkar, Tony Belli, Laura Mee, Aoife Neal, Hazel Smith, Emma Toman, Kamal Yakoub, Andrew Stevens, Mohamed Nour, Mycroft Halliwell â€“ Ewen , Austin Gomindes, Simon Meredith , Peter Welby-Everard , Babita Rajkumari, Tom Fowler, Madiha Azher, Victoria Siddons, Sikander Majid, Angus Selby, Navjit Kalsi, John-Paul Molesworth, Aileen Molesworth, Tom Hawthorne, Azan Majeed, Nasir Ali, Lisa Moody, Christopher Sheridan , Amy Clark, Natalie Dooley, Alexandra Newton-Cox, Jo Weston Price, Eslam Allam , Kate Clayton

Queen's Hospital
Darryl Wood, Lunik Sarder, Ignatius Postma, Maruteshwar Reddy, Dondorebarwe Sakutombo, Sam King, Helen Smith

Royal London Hospital
Ben Bloom, Raine Astin-Chamberlain, Imogen Skene, Kirsten Parkin, Noemi Caponi, Grace Tunesi, Nimca Omer, Alison Quinn, Jacqueline Sear

Royal Preston Hospital
Kirsty Challen, Louis Turrell, Tonileigh Sutcliffe-Whyte, Claire Pollington, Mark Verlander, Amanda Alty, Alexandra Williams, Sandra Sowden

Salford Care Organisation
Daniel Horner, Peter Kilgour, Samantha Dodds, Amber Sampson, Lisa Swindells, Aleksandr Valkov, Scott Beattie, Tracy Marsden, Reece Doonan, Nathan Butterworth, Daniela Santos, Stephanie Lee, Jane Perez, Kathryn Cawley

South Central Ambulance Service (SCAS)
Charles Deakin, Isabel Rodgriguez-Bachiller, Andrew Claxton, Helen Pocock, Martina Brown

SCAS ambulance stations: Nursling, North Harbour, Lymington, Winchester & Eastleigh, Hightown, Milton Keynes: Alan Delaney-Munn, Alex Borrington, Alex Orford, Ashlea Rowland, Ben Bridges, Ben Brown, Ben Cole, Bob Bell, Charles Mead, Charlie McGurk, Chris Vaughan, Claire King, Craig Jackson, Daniel Leadbetter, Daniel Marshall, Daniel Morrison, David Gates, David Kehoe, Emma Holford, Eoin Magee, Ethan Reed, Gareth Lines, Gary Painting, Goncalo Saboia, Hannah Tobin, Heidi Kemp, Helen Landrum, Hollie Craggs, Jaroslav Varga, Jennifer Galuszka, Jennifer Ray, Jeremy Bailey, Jim Edwards, Jonathan Phillips, Jonathan Sampson, Joshua Nicholls, Katherine Christie, Kymberly Barry, Lacey Lewington, Lauren Goss, Lliam Warren, Marc Stimpson, Matt Baillie, Matthew Boustred, Melody Pooles, Michael Vicary, Miles Magauran, Nicola Broomfield, Patricia Larcombe, Phoebe Dolton, Rachel Jepson, Richard Martin, Richard Maxon, Rob Mackenzie, Robert Mariniello, Ruben Warington-Banfield, Scott Jenkins, Shane Logan, Simon Mynett, Sophie Stewart, Sophy Savage, Steve Paffett, Susan McSheaffrey, Sven Shore, Thomas Roe, Zoe Stace

South East Coast Ambulance Service (SECAmb)
Julia Williams, Pete Eaton-Williams, Craig Mortimer

SECAmb ambulance stations: Paddock Wood, Ashford: Adam Line, Alan Hougham, Andrew Smith, Antony Bailes, Benjamin Stevens, Charlotte Arthur, Chris Coveney, Colin Doig, Colin Leedham, Daniel

Bensberg, Darren Wardle, David McQuillan, Elliot Williams, Emma Hulme, Gemma Hopkins, Grace Brenchley, Graham Picknell, Grant Payne, Hannah Knight, Heidi Wright, Ian Spencer, Jacek Sokulski, James Edwards, Janine Trice, Jay Watling, Jeff Humm, Joshua Guinane, Joshua Tompkins, Julian Macdonald, Kerri Morgan, Lamarah Harris, Laura Giurgea, Lee Emberley, Lewis Samways-Head, Louise Phillpott, Lucinda Ly, Luke Hamilton, Mark Lowe, Martha Tilling, Michael Stoker, Michal Pezda, Michelle Dyke, Michelle Skillington, Mitchell McQueen, Nakai Redman, Peter Elliott, Peter Kelly, Phillip Richardson, Rachel Barton, Richard Locke, Robert Goss, Robin King, Samantha Miller, Sean Edwards, Taryn Brown, Thomas Boreham, Thomas Myles, Thomas Rowland, Thomas Whateley, Tony Eyres, Victoria Findlay, Wendy Pearson, Zeke Riding

St George's Hospital
Heather Jarman, Will McGuinness, Claire Crofton, Faye Mahony, Jade Moseley-Rogers, Claire Seel, Louise Agyepong, Ashik Babu

St Helier Hospital
Rebecca Macfarlane, Lisa Evans, Marco Machado, Sumaya Huque, Nadeem Ishtiaq, Suzanne Goddard, Ansareen Untoo, Shilpa Gajjar, Anna Laurenson, Amir Hassan, Nilan Subra, Tim Oreo, Robert Tan, Richard Opom, Grace Blows, Manuel Rebolledo, Amy Matthews

St Thomas' Hospital
Laura Hunter, Nikhita Dattani, Emma Page, Montee Chan, Debbie Jegede, Tessa Raafat, Se-Yi Hong, Sahaj Sethi, Eline Degeetere, Amit Gaikwad, Mitchell Waters, Mathew Blundell, Lachlan Sund, Klara De Baerdemaeker, Trang Singhal, Yaseen Serry, Polly Keeling, Jenifa Jeyakumar, Charli Massey, Atul Pagad, Moysore Odukunle, Shailshree Vaidhya, Sakshi Sehgal, Bruno Coelho, Benjamin Trenwith

Whittington Hospital
Lucy Parker, Nicola Brown, Ben Flavell

William Harvey Hospital
Jonathan Leung, Andrew Gillian, Chris Woods, Sam Morgan-John, Daniel Sumner, James Rand, Heather Weston