Received: 3 August 2023 | Revised: 4 October 2023 | Accepted: 15 October 2023

DOI: 10.1111/bcp.15949

ORIGINAL ARTICLE

Adopting human factors in early phase and experimental medicine research: A nested pilot study observing controlled human infection with SARS-CoV-2

Helen E. Higham[1,2] | Lauren Morgan[1] | Cushla Cooper[3] | Julia Marshall[4] | Andrew Mawer[4] | Susan Jackson[4] | Raquel Lopez-Ramon[4] | Eileen Hughes[4] | Duncan Richards[3,5] | Helen McShane[4] | James N. Fullerton[3,5,6]

[1]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

[2]Department of Anaesthetics, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[3]NIHR Oxford Clinical Research Facility, University of Oxford, Oxford, UK

[4]Department of Paediatrics, University of Oxford, Oxford, UK

[5]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK

[6]Department of Clinical Pharmacology and Therapeutics, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Correspondence
Helen Higham, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK.
Email: helen.higham@ndcn.ox.ac.uk

James Fullerton, NIHR Oxford Clinical Research Facility, University of Oxford, Oxford, UK.
Email: james.fullerton@ndorms.ox.ac.uk

Funding information
University of Oxford; Wellcome Trust, Grant/Award Number: 222305/Z/21/Z

Aims: The influence of human factors on safety in healthcare settings is well established, with targeted interventions reducing risk and enhancing team performance. In experimental and early phase clinical research participant safety is paramount and safeguarded by guidelines, protocolized care and staff training; however, the real-world interaction and implementation of these risk-mitigating measures has never been subjected to formal system-based assessment.

Methods: Independent structured observations, systematic review of study documents, and interviews and focus groups were used to collate data on three key tasks undertaken in a clinical research facility (CRF) during a SARS CoV-2 controlled human infection model (CHIM) study. The Systems Engineering Initiative for Patient Safety (SEIPS) was employed to analyse and categorize findings, and develop recommendations for safety interventions.

Results: High levels of team functioning and a clear focus on participant safety were evident throughout the study. Despite this, latent risks in both study-specific and CRF work systems were identified in all four SEIPS domains (people, environment, tasks and tools). Fourteen actionable recommendations were generated collaboratively. These included inter-organization and inter-study standardization, optimized checklists for safety critical tasks, and use of simulation for team training and exploration of work systems.

Conclusions: This pioneering application of human factors techniques to analyse work systems during the conduct of research in a CRF revealed risks unidentified by routine review and appraisal, and despite international guideline adherence. SEIPS may aid categorization of system problems and the formulation of recommendations that reduce risk and mitigate potential harm applicable across a trials portfolio.

KEYWORDS
clinical trials, human factors, methodology, patient safety, translational research

The authors confirm that the Principal Investigator for this paper (the COV-CHIM01 study: ClinicalTrials.gov Identifier NCT04864548) is Professor H. McShane and that she had direct responsibility for patients.

1 | INTRODUCTION

Participant safety is the primary responsibility of those undertaking clinical research. During the early phases of clinical drug development and in experimental medicine studies the risk to participants is proportionately higher due to the comparative lack of information on the investigational medicinal product (IMP, when employed) or intervention, and any benefit indirect, as healthy individuals who may derive no therapeutic benefit are frequently enrolled. The need to reduce or mitigate risk through appropriate study design and conduct, and the presence of robust safety monitoring and governance, is thus imperative.[1,2]

In both most recent examples in which participants in early phase trials have been seriously harmed, Tegenero (TGN1412)[3] in 2006 and Bial (BIA 10-2474)[4] in 2016, the intervention was the primary source of injury, but the response to the emergency was suboptimal contributing to the overall harm. Issues related to preparedness, communication, training and standardization played a significant part in affecting the quality of the response. Recommendations and commentary from expert groups following these events has concentrated on the relevance of pre-clinical studies, their interpretation and translation, and subsequent trial design and conduct.[5–8] In contrast, there has been little focus on either the human factors that may influence a drug development programme and the studies that comprise it, nor the development of safer work systems within organizations and facilities that run clinical trials or host them, to protect future study participants and the staff involved in their care.[9]

Safety critical industries have invested significant resources in studying how adverse events manifest.[10] Current thinking supports moving away from regarding the human as the problem after a serious incident and instead analysing safety threats in the work system more broadly.[11,12] Derived from the field of complex systems,[13,14] this focus on systemic problems inhibits the unhelpful, reflexive response that sees 'human error' as the primary causal factor in safety incidents. This learning has now been extensively applied to the healthcare sector, where human factors methods have been employed to enhance team performance in crisis management and provide safer care in procedural areas with consequent improvement in clinical outcomes.[15,16] To our knowledge it has not been explicitly extended to research involving human participants.

Through structured observations during the conduct of one experimental medicine study employing a controlled human infection model (CHIM), we sought to identify the potential value of employing human factors methods to identify overt and latent risks in existing study protocols, the local work system and environment of a clinical research facility (CRF), and to generate practical recommendations that could improve safety.

What is already known about this subject

- Serious harm to healthy individuals volunteering to participate in clinical studies is rare but catastrophic when it occurs.
- Human factors methods can provide valuable insights into latent safety risks in healthcare environments.
- Their applicability to experimental clinical research and ability to generate effective recommendations in this context is unknown.

What this study adds

- Human factors methods can be utilized in a clinical research facility (CRF) to highlight previously unrecognized safety threats.
- Multidisciplinary team collaboration results in pragmatic interventions to mitigate potential harm to study participants and staff.
- Potentially transferable recommendations include improved standardization, and the use of checklists and simulation in CRFs.

2 | METHODS

We conducted a single-centre, single-trial, observational analysis, based at the NIHR Oxford Clinical Research Facility (OxCRF). This 13-bed CRF provides a resource for experimental and early phase clinical research across the Medical Sciences Division of the University of Oxford and Oxford University Hospitals NHS Foundation Trust (OUHT). The study observed was COV-CHIM01: A Dose Finding Human Experimental Infection Study With SARS-CoV-2 in Healthy Volunteers (NCT04864548, Department of Paediatrics, University of Oxford). This dose escalation challenge study sought to identify the dose of SARS-CoV-2 required to achieve a 50% infection rate in healthy volunteers, enabling discovery science and, if successful, facilitating the targeted evaluation of therapeutics in future studies. Selection of COV-CHIM01 for human factors evaluation was based on the incorporation of multiple complex protocol elements, the high level of multi-disciplinary working necessitated and the enhanced risk associated with non-compliance with specified standard operating procedures (SOPs) given the potential for transmission of infection.

Three phases of work were conducted: i) *Preliminary data gathering and task prioritization*: Staff from the OxCRF and Department of Paediatrics study team (COV-CHIM study team) were consulted on three separate occasions via a combination of interview, focus group and email to identify protocol elements that represented greater relative risk either due to complexity or risk of exposure to live virus. Relevance to research beyond the index study was also considered. ii) *Task analysis*: Three tasks were selected for inclusion: Inoculation of participants with the pathogen; in-room assessments of inoculated

participants by staff; and transfer from the OxCRF to the main OUHT hospital for study investigations. Two investigators (one clinician [H. H.], one non-clinical chartered human factors specialist [L.M.]) used structured observations[17–19] to analyse work procedures, observing three specific tasks and general work activities in real time, and assessing the usability of artefacts including equipment, SOPs and study protocols. The observations focused on capturing an understanding of 'work as done', and review of SOPs and other study documents on understanding 'work as imagined' (see Figure 1). Observations during the three tasks and for general work activities in OxCRF were categorized using a human factors framework designed for healthcare, the Systems Engineering Initiative for Patient Safety (SEIPS;[19,21,22] see Figure 2) Person, Environment, Task, Tools and technology (PETT) scan.[23] iii) *Designing recommendations*: This was undertaken collaboratively with Oxford Simulation Teaching and Research (OxSTaR), OxCRF and COV-CHIM study teams.

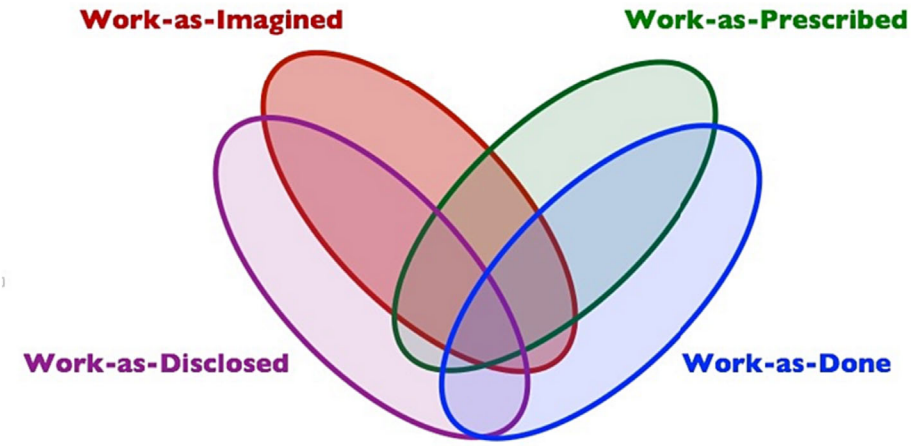

FIGURE 1 The varieties of human work. Conceptualizing human work is important when considering how outcomes are achieved and what impacts the success and/or safety of the task in hand. Shorrock has described four basic varieties of human work.[20] Work as done is, simply put, what actually happens in the workplace and is best analysed by direct observation; work as imagined is how people think work is done at the frontline and is influenced by various factors including past experience, knowledge of the work that is being undertaken and personal bias; work as disclosed is what people say or write about their work; and work as prescribed is the formal description (usually written, e.g., as an SOP) of how work should be done. The figure depicts the four basic varieties of human work (described by Shorrock[20]) revealing areas of overlap and of difference for each type.

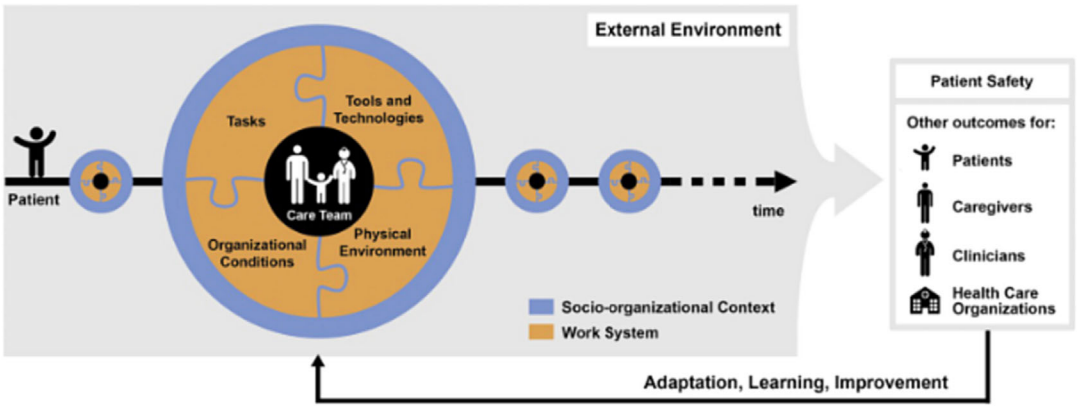

FIGURE 2 The Systems Engineering Initiative for Patient Safety(SEIPS). SEIPS[19,21–23] was designed by systems engineers and human factors scientists in collaboration with healthcare providers to be a framework for analysing healthcare systems, examining work processes and designing interventions to improve patient safety.The figure provides an overview of the model with patient at the centre of the healthcare system described within socio-organizational contexts. Key factors influencing patient safety are divided into people (e.g., clinical teams, family members or the patient themselves), environments (e.g., physical, cultural), tasks (which may involve multiple interdependent teams) and tools and technologies, all of which are influenced in turn by external environmental factors (e.g., regulatory bodies or government policy). The SEIPS model recognizes the adaptive nature of healthcare systems with a feedback loop from outcomes back into the work system. SEIPS 101[23] describes a series of simplified ways of using SEIPS to analyse work in healthcare. The PETT (People, Environments, Task, Tools and technology) scan is one example which can be used in many contexts to consider facilitators and barriers to safe practice (e.g., to examine tasks involved in a ward round or to analyse a safety incident and consider contributory factors). It was chosen for this study as it was designed to be straightforward to use in any clinical context.

Data collection visits were made between February and March 2022. Observers were embedded in the work environment and made all visits together, observations being undertaken once for each task. To mitigate the risk of the investigators being exposed to live virus during inoculation, a contemporaneous audio-visual feed was reviewed from a nearby office using the pre-installed OxCRF CCTV system and an additional microphone placed in the participant's room. No recordings were made. Direct observation of the transfer of participants to the hospital for CT scanning was deemed impossible due to the risk of investigator contact with infected participants and the potential for distraction of the study team en-route to the scanner. Consequently, these observations were made in real time using a simulated journey with a member of the study team acting as a study participant. Observations for each task ended after a period of reflection with OxCRF and COV-CHIM study team staff and study participants (if they wished) when comments about the procedure could be openly discussed and recorded. Informed consent was gained from staff and participants involved in each of the observed tasks. Trial documentation and protocols were reviewed both independently and in conjunction with trial staff to understand their perspective and interpretation. Specific points about the methodology for each task are summarized in Table 1.

To design and prioritize recommendations (Phase iii) five focus group discussions were facilitated by H.H. and L.M. with multidisciplinary staff from both OxCRF and the COV-CHIM study team. An additional summative discussion of the study results confirming agreement on recommendations was held including all staff and the leads for both OxCRF (D.R.) and the COV-CHIM study team (H.McS.).

The study represented a collaboration between OxSTaR (in the Nuffield Department of Clinical Neurosciences), OxCRF and the Department of Paediatrics. The human factors protocol was reviewed by the Research Governance Ethics and Assurance team at the University of Oxford and deemed not to require further ethical approval in addition to COV-CHIM01 (21/UK/0001). Informed consent for observation was obtained from all trial volunteers as well as OxCRF and COV-CHIM study team staff. No participant-identifiable data were collected. This human factors study was registered on the OUHT Ulysses platform (project number 7381).

TABLE 1 Description of observations recorded for three selected tasks required for the conduct of the COV-CHIM01 study undertaken in the OxCRF: participant inoculation, throat and nose swab and transfer to OUHT for radiological investigation (CT scanner).

Task	Specifics of data collection visit
Inoculation of participant with SARS-Cov2	Observations began before the virus was delivered and included: • Methods of informing staff on site (including those not directly involved in the task) that inoculation would be occurring • Team briefing pre-inoculation • Collection and delivery of virus to participant's room • Use of personal protective equipment (PPE) • Preparation of the participant for the procedure • Pre-procedure in-room checks • Inoculation process including use of SOPs and checklists • End-procedure exiting from the participant's room (including doffing PPE)
In-room procedure: throat and nose swab	Observations began before the COV-CHIM study team entered the participant's room and included: • Use of PPE • Collection of a sample from a throat and nose swab including use of SOPs • End-procedure exit from room (including doffing of PPE) • Recording and storing samples in freezer
Transfer to hospital site for CT scan	Observations of a simulated participant journey were made with a member of the COV-CHIM study team acting as the participant and included: • An initial verbal run-through of the path taken to the CT scanner in the OUHFT • Use of the same members of the team who would actually be involved in transferring participants to the scanner • Timing the whole journey, numbers of people contacted en-route, any environmental risk factors outside OxCRF

3 | RESULTS

3.1 | Observations

Overall observations revealed a high performing CRF with good collaborative leadership on site, and a clear focus on safety for participants and staff involved in clinical trials. Observations of general work activities in OxCRF revealed the following facilitators to safe practice:

- Physical spaces in the centre were clean and free from clutter/noise.
- The environment was secure, with swipe card access to key areas.
- OxCRF has the benefit of being outside the main hospital but within easy reach in case of emergency.
- Workplace culture was supportive, collaborative and friendly.
- Team-working skills were well developed.
- Communication between COV-CHIM study team members and study participants was clear and respectful.
- Inter-team communication between COV-CHIM study team members and OxCRF staff was unambiguous and well-structured.

The three tasks observed involved variable numbers of study staff at different times of day:

- Inoculation (time observed: 12:00), six study team members involved: two study nurses collected the virus, two study nurses and one study doctor undertook the task and one study nurse acted as a runner and stayed in the ante-room adjacent to the participant's room.
- Throat and nose swab (time observed: 14:00): three team members were involved: one study nurse in the room to undertake the procedure and two study nurses to check and store the samples.
- Transfer to CT scan (time simulated: 14:30): two study nurses accompany participants to the scanner. The simulation involved another nurse acting as the participant. The route took 11 min to walk, 20 people were passed at less than the contemporaneous recommended safe distance for COVID (2 m) for less than 10 s (i.e., extremely low risk encounters). The simulation was conducted much earlier in the day than study transfers would usually occur (scans are routinely done in the early evening), and all staff reported that there were far fewer encounters with bystanders after normal working hours.

Latent safety threats were identified in three broad areas: rule breaking and normalization of deviance, standardization (including use of checklists) and work system design.

3.2 | Rule breaking and normalization of deviance

There were several areas where the guidance in SOPs was either insufficiently or imperfectly described, or where the team were 'forced' to bend the rules to achieve the task. Examples are provided below:

1. Personal Protective Equipment (PPE): At the time of data collection, guidance on expected levels of PPE were available from multiple sources including the UK Health Security Agency, the National Institute for Care Excellence (NICE) CG139, the University of Oxford and the OUHT. In addition, the OxCRF had core prescribed PPE requirements (e.g., limits on staff within certain spaces and disposable surgical masks to be worn at all times within the unit) and the study stipulated supplementary needs (e.g., times at which certain levels of PPE are required). This resulted in differing baseline assumptions of PPE requirements between staff depending on usual place of work and conflicting guidance for team members to follow in specific circumstances. The consequence was situations where team members exposed to the same level of risk, for example when transporting the virus to the participant, were (by rule) expected to wear discrepant levels of PPE throughout the journey, and in relation to their co-located colleagues. The SOP failed to capture nuances of the process and thus confidence in the rule around PPE was eroded by visible inconsistencies (e.g., staff near to, but not holding, the contained live pathogen wearing lower levels of PPE). Equally, when transferring participants from the OxCRF to OUHT for scanning, the COVCHIM study team reported confusion around which requirement to adhere to (i.e., which took precedence) and were often, but not always, required to change their PPE to OUHT provided equipment without a clear biological rationale.
2. Use of signage: A 'do not enter' sign was placed on the door in advance of the inoculation taking place. Several team members were observed to go in and out of the participant's room whilst the sign was on the door, that is, the sign has no real utility for indicating the exact time when they should not be entering. The placement of the sign should be contemporaneous with the safety critical moment of transfer of the pathogen into the room. Rule-breaking is inevitable in this situation as staff learn use of the sign is misaligned with risk, and failure to proceed despite its presence would hinder trial conduct.
3. Participant transfer: During transfer to the CT scanner, team members were instructed not to touch any surface. However, unidentified impediments were observed as the doors in the OxCRF cannot be fixed in an open position. Consequently, the participant either held the door themselves, or the staff opened the door for them, leading to the rules on social distancing and infection control described in the SOP being broken.

3.3 | Standardization and the use of checklists

We observed an appreciation of the importance of standardization of tasks and a clear focus on using SOPs for key procedures during the trial. However, the SOPs were frequently lengthy (ranging between seven and 79 pages for amalgamated documents with multiple elements), and simplified checklists to accompany tasks such as inoculation were not available leading to the development of unapproved 'workarounds'.

We observed that the study team had designed checklists for use both pre-procedure and during inoculation (see Appendix A). However, these checklists were not designed according to human factors principles[24,25] and were cumbersome to use. For instance, the in-room checklist for inoculation was an adapted SOP containing over 50 steps rather than an optimized, task-focused list of safety critical steps, and was being used in paper form in the room with live virus.

A standardized approach to the management of potentially life-threatening emergencies such as anaphylaxis is important when teams are interacting on an ad hoc basis. Despite the OxCRF having the full complement of emergency equipment and appropriate signposting, the anaphylaxis box was noted to be different from the one used routinely in the OUHT. This may present unnecessary confusion for staff arriving from the hospital to assist in an emergency. Issues with lack of a standardized approach to PPE have already been described above.

3.4 | Work system design—SEIPS PETT scan

Work system factors were analysed using a SEIPS PETT scan[23] for all three tasks. Results for participant inoculation are shown in Table 2 and for general work activities in Table 3 (for in-room assessment and participant transfer to CT; see Data S1). The PETT scans revealed barriers and facilitators to safe practice in each category, including the issues around enforced rule breaking and standardization identified above.

Analysis of protocolized tasks identified that the infrastructure for research teams working within the OxCRF is not yet optimized. For example, no specified quiet area for rest was available. Staff working overnight have found workarounds (e.g., by using a separate clinical space) but the importance of adequate rest is well recognized.[26,27] Potential alterations to staff areas to improve privacy and adaptations to audio-visual systems to enhance the ability to observe and communicate with participants when necessary (without significantly impacting their privacy) were flagged.

Over the course of the study several additional matters arose which, whilst not formally observed, may have represented potential safety risks. This is exemplified by the unexpected occurrence of groundworks outside the main CRF entrance, which would have impeded access in a clinical emergency (see Data S2).

Overall, risks were evident in all SEIPS work system categories and their identification informed recommendations to improve safety.

3.5 | Recommendations

Recommendations were aligned with SEIPS work system factors and designed in accordance with SMART (specific, measurable, achievable, realistic and time bound) principles[28] to mitigate the observed safety risks. Fourteen initial recommendations were co-created and, following focus group review, seven were felt to be implementable within a short timeframe and to be sustainable for future studies (Table 4).

4 | DISCUSSION

A pre-eminent feature of safety critical organizations is the 'implementation of highly structured approaches to safety management' such that they are 'proactively identifying, assessing, mitigating and

TABLE 2 Summary of barriers and facilitators to the conduct of a specific exemplar task—participant inoculation with SARS-CoV-2—detailed in the COV-CHIM01 protocol and carried out by the COV-CHIM study team and OxCRF staff.

SEIPS work system factors	Participant inoculation
People	*Barrier*: Some newer members of team unfamiliar with certain aspects of task. *Facilitator*: Supportive working environment, friendly and respectful team.
Environment	Physical environment: *Barrier*: Difficult for staff in participant's room to negotiate bed and table; find comfortable positions to undertake task; see wall clock and perform the checks. *Barrier*: Difficult for member of staff in anteroom to see and hear what was happening during inoculation. *Barrier*: Anteroom too small to support donning and doffing of PPE without risk of contamination. *Facilitator*: Large, well-lit spaces which could be adapted. Socio-organizational environment: *Barrier*: Regular meeting in the laboratory underway at time of inoculation. *Barrier*: Miscommunication between clinical team and laboratory upstairs led to delay in virus arrival. *Barrier*: Communication unclear with staff not involved in inoculation (e.g., cleaning staff were difficult to find and inform at the time of inoculation which led to delay). *Facilitator*: Structured team briefings already in use—could be adapted. External environment: *Barrier*: Conflicting and rapidly changing advice during course of pandemic from national bodies on levels of personal protective equipment (PPE).
Task	*Barrier*: Task required several steps to be taken in order—process not supported by checklist. *Barrier*: Team members reported being unclear on precise time virus was in OxCRF. *Barrier*: Use of PPE not standardized across team members with lack of clarity over exactly what to wear in different areas, for example, corridors. Observed different ways of donning and doffing PPE. *Facilitator*: Adaptability of team members.
Tools/technology	*Barrier*: Lengthy study protocol used as a form of checking tool in participant's room. Protocol cumbersome and time-consuming with more than 50 steps. Paper based records used—difficult to sort through and keep clean. *Facilitator*: Study team already designing simplified checklist. *Barrier*: 'Do not enter' sign placed on door to anteroom too early, therefore, ignored before the virus arrived. *Barrier*: No other visible indication that virus was in OxCRF. *Barrier*: No technology for two-way communication between participant's room and areas outside. *Facilitator*: Easy, non-intrusive solution found in collaboration with OxCRF and the COV-CHIM study team to provide better in-room audio-visual facilities during study.

Note: These have been systematically identified and categorized by work system factors using the SEIPS PETT scan method.

TABLE 3 Summary of barriers and facilitators to the general work activity of the OxCRF categorized by work system factors according to a SEIPS PETT scan.

SEIPS work system factors	Examples of latent risks in general work activity in OxCRF
People	*Barrier*: Diverse group of healthcare professionals involved in study, some had trained in different healthcare cultures, some did not have English as a first language. *Barrier*: Some newer members of study team were uncertain about aspects of tasks. *Facilitator*: Inclusive and supportive teams with a visible focus on collaborative teamwork.
Environment	Physical environment: *Barrier*: Groundworks underway outside OxCRF causing restricted access to both entrances during observation period. Unclear what measures were in place for access in emergency or if go/no-go criteria described. *Barrier*: Facilities for research teams not optimal yet, for example, no designated area for overnight rest; lights come on automatically with movement; no handwashing facilities in coffee room. *Facilitator*: Large, well-lit spaces which could be adapted. *Barrier*: Visibility and communication into participants room hampered by room design. Socio-organizational environment: *Barrier*: Communication required between different teams (e.g., OxCRF team and study teams); areas on site (e.g., OxCRF and laboratory); areas in different organizations (e.g., OxCRF and hospital scanner). Communication about certain aspects of tasks unclear (e.g., route to be taken to CT scanner). *Facilitator*: Recognition of the importance of clear communication and observation of regular closed-loop communication between team members. *Barrier*: Use of checklists not routine. *Barrier*: Training for emergency situations (e.g., anaphylaxis, cardiac dysrhythmia) available (BLS is mandatory for all staff) but not 'low dose—high frequency' model. *Facilitator*: Strong desire within OxCRF and the COV-CHIM study team to improve checklists and training.
Task	*Barrier*: No explicit go-no-go criteria in trial protocol or OxCRF SOPs to highlight criteria for halting specific task/trial. *Barrier*: Communication difficult from participant's room to outside. *Facilitator*: Options available to modify communication systems in OxCRF.
Tools/technology	*Barrier*: Paper record-keeping common. *Barrier*: Signage for procedures which may incur risk (e.g., inoculation) not standardized or clearly visible and in paper form. *Barrier*: Communication between areas variably supported with modern telecommunication tools. *Facilitator*: Options available to modify communication systems in OxCRF.

monitoring risk'.[29] A variety of human factors methods exist to explore and analyse work systems and processes. Some have been developed in other settings[30,31] and some adapted or specifically designed for healthcare.[19,32] This study has used SEIPS[33] to analyse safety risks during the conduct of an experimental medicine study in an academic CRF because it was designed specifically for healthcare contexts and has been adopted for wider use in the NHS.

The analysis of work as a human endeavour has been the subject of studies in social and engineering sciences over the past 70 years.[34,35] 'Work as done' commonly differs from 'Work as imagined' (see Figure 1) and that discrepancy increases as individuals become more distant from the actual work environment spatially, temporally and experientially. Problems arise when managers or policymakers, or in the case of clinical research, those designing studies, make assumptions about activity and formulate protocols and guidelines which describe how work should be performed, without absolute certainty that what one imagines is achievable will actually be deliverable.[36] This inevitably leads to rule-breaking by the humans undertaking the tasks in order to get the work done.[10]

Despite the existence of a detailed risk assessment for the COV-CHIM study protocol, a Control of Substances Hazardous to Health (COSHH) risk assessment and the evident focus on participant safety from the staff of both the facility hosting the observed study (OxCRF) and those who conducted it (COV-CHIM study team), we found that structured observations incorporating human factors methodology provided additional insight into latent risks in the protocol as written, the CRF facility itself and the interaction between the two, that had not been identified a priori by either standard processes, or peer review, institutional, ethical and sponsorship appraisal. In addition, confusion in, or deviations from, expected practice (often unavoidable) and the development of local workarounds was catalogued: behaviour that study and facility leadership were unaware of via conventional pathways. Use of the SEIPS PETT scan aided the design of recommendations to rectify or mitigate these risks by the multidisciplinary team and their prioritization for implementation based on the established hierarchy of effectiveness of corrective actions[37] in which physical interventions (e.g., pathway or equipment redesign) are considered most effective; procedural interventions (e.g., automation or use of checklists) are considered moderately effective, and person-based interventions (e.g., warnings or training) are considered weak.[37]

Given the single-centre, single-study basis of our work, it is inevitable that the specific findings described here will not be wholly generalizable to other facilities and research programmes. However, this was not the intent of the study. Instead, we sought to understand whether the extension of human factors methods to early phase and experimental medicine research generated meaningful, actionable

TABLE 4 Summary of 14 initial recommendations co-created by OxSTaR, COV-CHIM study team and OxCRF to mitigate potential risks to study conduct, staff or clinical research participants identified via structured observation.

No.	SEIPS work system factors	Recommendation
Rule breaking and normalization of deviance		
1	*People*	*Requirements for induction of new staff and communication of changes to existing staff should include simulated walkthroughs of critical tasks and multimodal communication tools (e.g., email, WhatsApp groups, staff briefings). Where tasks are likely to be low frequency, they may be supported by SOPs. Ensure staff coming to the centre understand that the use of checklists is 'business as usual' in OxCRF and direct them to guidance and training available for bespoke checklists.*
2	*Task*	*Clarify and standardize PPE requirements throughout OxCRF, focusing on likely points of proximity to pathogens, as well as specific tasks. Requirements may vary according to activity in OxCRF. This could be communicated at daily briefings.*
3	Tools	Standardize the format of signage for key procedures in the OxCRF. Consider utilizing technology to support standardized, visual confirmation throughout OxCRF that higher risk trial processes are underway (e.g., lit signs in radiology when x-ray is in use).
Standardization and use of checklists		
4	*People*	*Review of training offered in the OxCRF including frequency, types of training (e.g., online, in-situ simulation) and quality assurance processes. Ensure training is offered in the use of checklists.*
5	*Task*	*Standardize the anaphylaxis box and instructions with those in use in the OUHFT.*
6	*Tools*	*Develop an OxCRF template for checklist design. Trials teams should be encouraged to design checklists for safety-critical procedures using guidance in current SOPs. Ultimately a 'quick reference handbook' (QRH) much like the national QRH for anaesthetics could be developed.*
Work system factors—PETT scan		
7	*People*	*Team communication to include review of activities at daily briefing (a safety huddle) which specifies adaptations to activity required, e.g., adjusting pathogen collection times to avoid scheduled lab meetings.*
8	*Environment (physical)*	*Working with study teams, consider if there is better placement within room of key items (e.g., the clock). Explore if doors in OxCRF have option to remain open without need for physical contact.*
9	Environment (physical)	Consider changes to the environment that would improve visibility and audibility during procedures, for example, adapt CCTV technology already in use to allow better monitoring of procedures during the project. An intercom system between participant's room and corridor would support key tasks, and if more harmful agents being tested, would improve communication with the participant.
10	Environment (physical)	Review of possibilities for donning and (more importantly) doffing PPE in an alternative area.
11	Environment (physical)	Review facilities for staff on site in collaboration with study teams.
12	Task	Consider detailing 'go, no-go' criteria for every study group, and ensure they are understood by all members of the team. Specific communication options (e.g., buzzer) could be used as alerts.
13	Tools	Switch to electronic recording system for sample storage.
14	Tools	Use simulation as a tool to explore pathways and novel procedures and understand latent risks before they become real.

Note: These have been categorized using a SEIPS PETT scan. The seven recommendations to be prioritized for immediate action are highlighted in italic script.

results to improve participant and staff safety. Our experience supports this assertion but clearly requires both extension and replication. Specific areas that warrant prioritization due to their likely commonality across study type and relevance to multiple CRFs are discussed below.

4.1 | Rule breaking and normalization of deviance

Accepted and normalized rule 'breaking' is a part of everyday human activity,[38] but it can lead to a shift in the safety culture of a team or unit over time. We observed areas where the guidance provided to researchers and clinical support staff was either not clear, or 'forced' the team to bend the rules to achieve protocolized tasks. This was exemplified by variability in the stipulated requirements around the use of PPE and the inaccurate use of the 'do not enter' sign during live virus inoculation. Whilst such instances may be dismissed as trivial if not immediately elevating risk to staff or participants, the wider consequences include variability in practice, erosion of trust in trial documentation or procedures (extending beyond the index study) and the development of unapproved (or unacknowledged) workarounds with potentially unintended consequences. Adoption of a systemic

approach that actively seeks to pre-identify discrepancies between work as imagined and work as done, and a blame-free culture that enables enforced rule breaking to be openly discussed, should counter these concerns. For instance, the use and acceptance of clear and accurate indicators of risk that are rigidly controlled and adhered to (e.g., an amber light over participants' rooms and in corridors when live pathogen was present, akin to imaging departments employing ionizing radiation) would cement trust and promote safety.

4.2 | Standardization and the use of checklists

Standardization supports workers in undertaking often difficult tasks by reducing the attentional demands normally required to achieve these, freeing up cognitive resources for dealing with complex issues that can evolve in dynamic work environments. There has, however, been noticeable resistance to standardization in healthcare, not least because efforts at standardization may be poorly thought through, and often irrelevant to the complex, nuanced, sociotechnical systems in which healthcare professionals undertake their duties.[39,40] Checklists are a form of cognitive aid which have gained widespread acceptance in safety critical industries and are becoming more prevalent in healthcare both for elective and emergency situations.[24,25,41,42] There are design rules for effective checklists[41,43] including standardized language and layout, and a focus on including *only* the key safety-critical steps of a task. When used properly, checklists reduce cognitive load, protect against forgetfulness and minimize omission of key steps.[44]

Standardization of key procedures in OxCRF and by the COV-CHIM study team was evident during the study period, as was the use of checklists, both those designed and approved in advance and those generated in response to perceived deficiencies. Despite face validity, these processes were evidently suboptimal, with improvements in design being required in advance of study delivery and to deal with issues arising during study conduct. The Association of Anaesthetists in the United Kingdom has designed a Quick Reference Handbook (QRH)[45] to support improved safety in anaesthetic practice which adheres to these design principles (see Appendices B and C). These principles will now be used to support the development of a QRH for safety critical tasks and emergency situations (such as anaphylaxis) in this trial and others conducted in the OxCRF, an approach that may be mirrored in other units.

4.3 | Work system design—environmental issues

The design of physical spaces has been shown to play an important role in work efficiency and safety,[46] as well as staff satisfaction in industry and business, including in healthcare environments.[47,48] Our observations revealed constraints on safety induced by the local physical environment in the OxCRF. Whilst some were amenable to rapid change (e.g., repositioning a clock or a bed for ease of use/access) others would require more time and resources to rectify (e.g., electronic door controls). These findings suggest that, whilst clearly necessitating local appraisal and tailored solutions, the interaction between individuals (both staff and participants) and their environment should not be ignored whether persistent (e.g., the need for appropriate overnight rest areas for staff) or temporary (e.g., as here, groundwork transiently preventing emergency access). Of note, the COV-CHIM study was the first to employ the redeveloped OxCRF and this may have influenced some of our findings.

4.4 | Simulation

Several latent risks were observed which would be amenable to interventions using simulation. Although training is seen as a weak intervention,[37] there is good evidence supporting improvements in team performance and skill retention using simulation-based education in a 'low dose, high frequency' model.[15,49,50] Whilst simulation training is regarded as standard in many CRFs (including OxCRF) to support staff in maintaining and developing skills for the management of emergency situations, we identified opportunities to better design and focus the scenarios to fit local practice, address skill gaps, focus on the most likely clinical situations that would be faced by staff (e.g., tailored to ongoing or imminently opening studies) and for these to be offered more frequently than is routinely recommended by the UK CRF network.

Simulation is also a useful tool to test work systems, pathways and environments and has been used in a variety of clinical settings including emergency departments,[51] maternity units[52] and for major incident responses.[53] The simulated transfer of a participant to the CT scanner in this study revealed several issues including the risk of transfer of pathogens to door surfaces and uncertainty around the exact route to be taken. Simulated walkthroughs of tasks or procedures could be extended to reveal further potential safety threats and allow mitigations to be put in place pre-emptively.[54]

4.5 | Study limitations

In addition to the limited direct transferability of the specific safety issues and recommendations identified in this study to other research programmes and units, there was a limited time frame during which to undertake observations in OxCRF. We chose to restrict the study to three core tasks based upon initial consultation and scoping work that identified not only higher intrinsic complexity (and hence risk), but also their likely repeated use in future experimental medicine studies to enhance the applicability of our findings. It is possible that, had the full range of study activities been examined and a longer period for observation been permitted, we would have revealed additional latent safety issues. As with any observational data collection it is possible that relevant data were missed through distraction, cognitive overload or were affected by observer bias. This risk was reduced by using two independent observers experienced in teaching and undertaking observational research. Data were also collected by both

observers contemporaneously, with comparison of, and agreement on, findings. Due to the risk of live virus transmission, one of the observed tasks had to be simulated rather than involve enrolled participants, potentially inducing behavioural artefacts.

Participants gave informed consent to our observations and were offered the opportunity to comment as they wished. For the purposes of this pilot work, it was not practical to ask for more participant engagement. However, in future it would be valuable to achieve a more active role for participants both in study design and delivery.

5 | CONCLUSIONS

It is widely recognized that humans in the workplace create safety far more than they erode it. Human capacity for recognizing problems and adjusting behaviours and actions in the moment will almost always prevent an accident rather than cause one.[55] This premise was strongly supported in our observations of work processes in OxCRF. We observed the type of attributes and behaviours that support a strong safety culture in both the leadership teams and staff working in the centre including: encouraging and valuing diversity of opinion; a constructive dialogue about risk and an acceptance that just because processes are running smoothly in the moment, they may not do so reliably in future. It is this pro-active approach to safety that gave rise to this study in the first place.

CRFs are operated by NHS Trusts, pharmaceutical companies, contract research organizations or academic institutions, routinely staffed by a core team of healthcare professionals supplemented by trial-specific staff and charged with the delivery of multiple externally-generated protocols, often concurrently. This environment, especially during periods of high activity where IMP or interventions with divergent risk profiles are being evaluated, presents unique challenges where risk is concerned, and it is therefore vitally important to have robust safety frameworks in place that can apply across studies. Whilst the tool traditionally perceived to guarantee this is adherence to guidelines and regulations (with accompanying documentation), there is real danger these distract from core, often common sense, measures that involve consulting with the correct stakeholders with the relevant training, experience and local knowledge to instigate proportionate and focused measures to mitigate risk to participants.[56,57]

This is the first time, to our knowledge, that human factors methods have been explicitly used to analyse work systems in a CRF and protocol elements of an experimental medicine study to provide recommendations that improve the safety of clinical research. Our findings support the further investigation and validation of their value in this context with a view to routine implementation, not just in retrospect to the investigation of safety incidents, but proactively to help avert them.[9]

AUTHOR CONTRIBUTIONS

James N. Fullerton conceived the study. Helen E. Higham and Lauren Morgan designed and performed the research and analysed the data. Helen E. Higham, James N. Fullerton and Lauren Morgan drafted the manuscript, which was edited by Cushla Cooper, Helen McShane and Duncan Richards and reviewed by all authors. Julia Marshall, Andrew Mawer and Susan Jackson were Trial Clinicians for the COV-CHIM01 study and took part in the research. Raquel Lopez-Ramon was the Research Matron overseeing all nursing aspects of the COV-CHIM01 study and Eileen Hughes was the Research Nurse.

ACKNOWLEDGEMENTS

The Climax donation to the University of Oxford funded the reported work. The Wellcome Trust funded the COV-CHIM01 study for which the University of Oxford acted as sponsor. The authors would like to acknowledge the contribution of the full COV-CHIM study team, all staff members at the OxCRF and the technical and administrative team in OxSTaR. We would also like to thank all the individuals who volunteered to participate in the COV-CHIM01 study, especially those who agreed to be observed as part of this nested pilot project.

CONFLICT OF INTEREST STATEMENT

R.L.R. and S.J. have previously contributed to intellectual property licensed by Oxford University Innovation to AstraZeneca. All authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Helen E. Higham https://orcid.org/0000-0001-5796-0377

James N. Fullerton https://orcid.org/0000-0002-4855-9255

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How to cite this article: Higham HE, Morgan L, Cooper C, et al. Adopting human factors in early phase and experimental medicine research: A nested pilot study observing controlled human infection with SARS-CoV-2. *Br J Clin Pharmacol*. 2024; 90(7):1586-1599. doi:10.1111/bcp.15949

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

APPENDIX A

Checklist designed by multidisciplinary COV-CHIM study team for inoculation procedure. Checklists are a form of cognitive aid and should not be used as a record (which should be kept separately). There are some core principles of good design for checklists including standardization of language, layout and colour, inclusion of only the safety-critical steps in a procedure/task and training to embed appropriate use by team members.

Inoculation Safety Checklist	**Controlled Human Infection Model Oxford**			
Completed by runner	**Date:**	**Room:**	**Participant ID:**	**Order of inoculation** *(e.g 1st out of 4):*	
	Study Group:	**Planned Dose:** *(confirmed with study clinician and check allocation log completed)*		**Vaccination status:**	
	Have the staff roles been indentified?	**Doctor:**	**Runner:**	**Nurse 1:**	**Nurse 2:** *(If applicable)*
Completed by nurse 1	**Step 1 preparation** (outside participant's room)	**Step 2 Pre-procedure** (In the participant's room):	**Step 3: Sign Out with Doctor Post-procedure** (In the participant's room):	**Step 4: Final Sign Out Post-procedure** (In the participant's room)	**Team Debrief Any concerns raised by the team? (anotate below)**
	Volunteer eligibility CRF completed by doctor ☐	Wall-mounted Oxygen and suction system checked ☐	All documentation completed ☐	Hard surfaces cleaned with Clinnell wipes ☐	
	Challenge authorisation signed by doctor ☐	Identity of the participant checked and consent confirmed. ☐	All instruments cleaned as per SOP ☐	e-diary completed and reviewed ☐	
	Challenge paperwork corresponding to intended dosing available ☐	Participant's allergy status checked ☐	Instructions provided to participant ☐	All documentation completed ☐	
	All equipment for inoculation checked and confirmed (see SOP for full list) ☐	PPE available for participant (apron and goggles) ☐	Vial safely returned to runner according to protocol ☐	No safety concerns, safe for nurse to leave the room as per inoculation SOP ☐	
	Emergency and safety equipment available (Anaphylaxis box, Resuscitation trolley Biohard spill kit, Dry ice spill kit, PPE trolley) ☐	Bed position, bed draped and room cleared ☐	No safety concerns, safe for doctor to leave the room as per inoculation SOP ☐		**End of session**
	Appropriate PPE according to role available (Level 1 PPE runner, level 2 doctor and nurse) ☐	Negative pressure re-checked ☐			
	Negative pressure inside the room confirmed and no red 'fault' light in lobby ☐			Clinical waste double bagged and tagged ☐	**Doctor signature**
Completed by runner	Ok to proceed with collection of SARS-Cov2 vial(s) from the lab into the unit ☐		SARS-COv2 vial(s)returned to the dry ice, documentation completed ☐	Inoculation waste collected and sent for autoclave ☐	**Nurse 1 signature**
	On arrival of SARS-Cov2 vial(s) in the unit, CO2 monitor and temperature of dry ice checked, documentation completed ☐		Move to next participant's room if applicable/ if not applicable, return vial (s) to OVG lab ☐	Enhanced cleaning of room completed ☐	**Runner signature**

APPENDIX B

Association of Anaesthetists checklist for anaphylaxis (one of 26 checklists in the Quick Reference Handbook) subject to Creative Commons licence CC BY-NC-SA 4.0.

3-1 Anaphylaxis v.5

- Unexplained hypotension
- Unexplained bronchospasm *(wheeze may be absent if severe)*
- Unexplained tachycardia or bradycardia
- Angioedema *(often absent in severe cases)*
- Unexpected cardiac arrest where other causes are excluded
- Cutaneous flushing in association with one of more of the signs above *(often absent in severe cases)*

START

1. Call for help. Note the time. Stop or do not start non-essential surgery.
2. Call for cardiac arrest trolley, anaphylaxis treatment pack and investigation pack.
3. Remove all potential causative agents and maintain anaesthesia.
   - Important culprits: antibiotics, neuromuscular blocking agents, patent blue.
   - Consider chlorhexidine as cause (impregnated catheters, lubricants, cleansing agents).
   - Consider i.v. colloids as a possible cause.
   - Change to inhalational anaesthetic agent (if not already).
4. Give 100% oxygen and ensure adequate ventilation:
   - Maintain the airway and, if necessary, secure it with tracheal tube.
5. Elevate patient's legs if there is hypotension.
6. If systolic blood pressure < 50 mmHg or cardiac arrest, start CPR immediately.
7. Give drugs to treat hypotension (Box A):
   - **Hypotension may be resistant and may require prolonged treatment.**
   - Give adrenaline bolus and repeat as necessary.
   - Consider starting an adrenaline infusion after three boluses.
   - If hypotension resistant, give alternate vasopressor (e.g. metaraminol, noradrenaline infusion +/- vasopressin)
   - Give glucagon in ß-blocked patient unresponsive to adrenaline.
   - Hydrocortisone and chlorphenamine are no longer part of acute treatment (Box C)
8. Give rapid i.v. crystalloid:
   - 20 $ml.kg^{-1}$ initial bolus, repeated until hypotension resolved.
   - Fluid requirements may be significant
9. If bronchospasm is persistent, consider → **3-4**
10. Take 5-10 ml clotted blood sample for **serum tryptase** as soon as patient is stable.
    - Plan for repeat sample at 1-2 hours and >24 hours.
11. Plan transfer of the patient to an appropriate critical care area. Note tasks in Box D.
12. Prevent re-administration of possible trigger agents (allergy band, annotate notes/drug chart)

Box A: DRUGS TO TREAT HYPOTENSION IF CARDIAC ARREST → 2-1

- Adult adrenaline: i.**v.** 50 µg (= 0.5 ml of 1:**10 000**)
  i.**m.** 0.5 mg (= 0.5 ml of 1:**1000**) *if i.v. not possible*
- Paediatric adrenaline: i.v. 1.0 $\mu g.kg^{-1}$ (0.1 $ml.kg^{-1}$ of 1:**100 000**) [1:**100 000** solution made by diluting 1 ml of 1:**10 000** up to 10 ml]
- If no i.v. access, intraosseous adrenaline dose same as i.v.
- Suggested adrenaline infusion regimes (adult):
  5 mg in 500 mL dextrose = 1:**100 000**, titrate to effect
  3 mg in 50 mL saline. Start at 3 $ml.h^{-1}$ (= 3 $\mu g.min^{-1}$), titrate to maximum 40 $ml.h^{-1}$ (= 40 $\mu g.min^{-1}$)
- Glucagon (adult): 1 mg, repeat as necessary
- Vasopressin (adult): 2 units, repeat as necessary (consider infusion)

Box B: CRITICAL CHANGES

CARDIAC ARREST → QRH SECTION 2-1

Box C: HYDROCORTISONE and CHLORPHENAMINE CHANGES

AFTER initial resuscitation:

- Consider steroids for refractory reactions or ongoing asthma/shock.
- Antihistamines (preferably oral, non-sedating) can be given for skin symptoms.

Box D: DON'T FORGET

- Repeat testing for serum tryptase at 1-2 hours and >24 hours.
- Liaise with hospital laboratory about analysis of samples.
- Liaise with department anaphylaxis lead regarding referral to a specialist allergy or immunology centre to identify the causative agent (see www.bsaci.org for details).
- Inform the patient, surgeon and general practitioner.
- Report to MHRA (https://yellowcard.mhra.gov.uk).
- NAP6 online resource **including anaphylaxis follow-up packs**: http://www.nationalauditprojects.org.uk/NAP6-Resources#pt

3-1

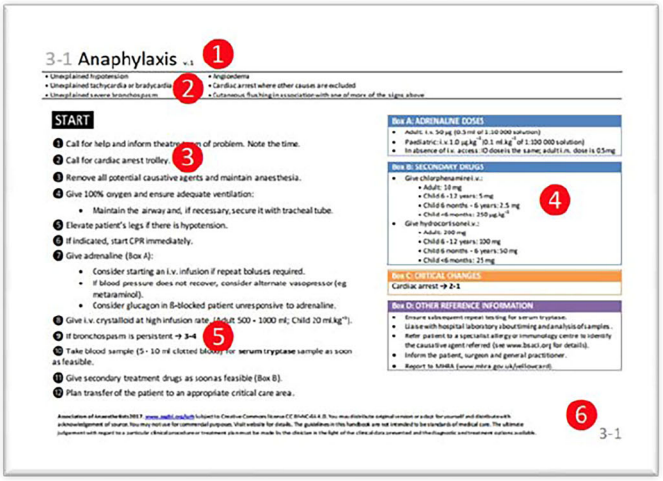
APPENDIX C

Instructions for use of checklists in Association of Anaesthetists Quick Reference Handbook.

Instructions for use

The QRH is intended for use by individuals who are familiar with it and who are practised in its use. See www.aagbi.org/qrh for further details on implementation.

Each guideline follows the same format:



(1) Guideline number, name and version number.
(2) A brief description of the clinical situation for which the guideline is written.
(3) The body of the guideline.
(4) Call out boxes, which may be referred to in the body text.
    - Orange = critical changes
    - Blue = drug doses
    - Green = CPR information
    - Black = equipment instructions
    - Purple = other reference information
(5) A guideline may suggest changing to one of the other guidelines, like this: → **2-1**
(6) The guideline number is repeated for easy finding without need for a tabbed folder.

Each guideline should be used in the same simple way.

- **Start at START.**
- **Work through the numbered bullet points in order.**
- **Where indicated, refer to the call out boxes on the right.**
- **Where indicated, move to another guideline.**

We recommend:

- One person should read the guideline aloud; they should NOT also be the person performing the actions.
- The reader should ensure that the guideline is followed systematically, thoroughly and completely and that steps are not omitted.
- Whenever experienced help arrives, consider delegating leadership to them: they have a fresh pair of eyes and may be able to make a more clear-headed assessment.