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Upskilling health and care workers with augmented and virtual reality: Protocol for a realist review to develop an evidence-informed programme theory

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3	1	ABSTRACT
4 5	2	
6	3	Introduction
7	4	Augmented reality (AR) and virtual reality (VR) are increasingly used to upskill health and care
8	5	providers, including in surgical, nursing and acute care settings. Many studies have used AR/VR to
9	6	deliver training, providing mixed evidence on their effectiveness and limited evidence regarding
10	7	contextual factors that influence effectiveness and implementation. This review will develop, test and
11		
12	8	refine an evidence-informed programme theory on what facilitates or constrains the implementation
13	9	of AR or VR programmes in health and care settings and understand how, for whom and to what
14 15	10	extent they 'work.'
16	11	
17	12	Method and analysis
18	13	This realist review adheres to the RAMESES standards and will be conducted in three steps: theory
19	14	elicitation, theory testing, and theory refinement. First, a search will identify practitioner, academic
20	15	and learning and technology adoption theories from databases (Medline, SCOPUS, CINAHL,
21	16	EMBASE, Education Resource Information Centre, PsycINFO and Web of Science), practitioner
22 23	17	journals, snowballing and grey literature. Information regarding context, mechanism and outcome will
23	18	be extracted. A narrative synthesis will determine overlapping configurations and form an initial
25	19	theory. Second, the theory will be tested using empirical evidence located from the above databases.
26	20	Quality will be assessed using the Mixed Methods Appraisal Tool (MMAT), and relevant information
27	21	will be extracted into a coding sheet. Third, the extracted information will be compared to the initial
28	22	programme theory, with differences helping to make refinements. Findings will be presented as a
29	22	
30 31		narrative summary, and the MMAT will determine our confidence in each configuration.
32	24	
33	25	Ethics and dissemination
34	26	Ethics approval is not required. This review will develop an evidence-informed programme theory.
35	27	The results will inform and support AR/VR interventions from clinical educators, healthcare
36	28	providers and software developers. Upskilling through AR/VR learning interventions may improve
37	29	quality of care and promote evidence-based practice and continued learning. Findings will be
38 39	30	disseminated through conference presentations and peer-reviewed journal articles.
40	31	
41	32	KEYWORDS
42	33	healthcare; learning; simulation; virtual reality; augmented reality; realist review
43	34	
44	35	STRENGTHS AND LIMITATIONS OF THIS STUDY
45 46	36	• The realist approach helps to understand the contextual factors that shape the implementation
40 47	37	and impact of AR/VR interventions to upskill professionals in health and care settings.
48	38	 The programme theory may be theoretically transferable, as it includes literature from various
49	39	health and care contexts.
50		
51	40	• The inclusion of the MMAT will help stakeholders use the theory by stating the extent to
52	41	which we are confident in each configuration.
53 54	42	• This realist review focuses on AR and VR, so may need to be modified to apply to other
54 55	43	digital simulation technologies.
56	44	• Literature included in this review is limited to that published in English.
57	45	
58	46	WORD COUNT: 3,990
59	47	
60		

INTRODUCTION

Upskilling in the health and care workforce

Upskilling through continuous learning and development is important in any business, to improve skillsets, advance practice and close gaps in knowledge. Upskilling is the process of learning new skills or refining existing skillsets to enable employees to continue practising with ease[1]. For health support and care workers, upskilling ensures that their work is safe and aligns with best practice guidelines, as they often receive variable and inconsistent training, as non-registered staff[2, 3]. Upskilling, in this sense, is therefore essential for providing consistent and high-quality care. Additionally, this promotes workforce flexibility and enables for the delegation of skills, when systems experience a shortage of staff[4]. Within the provision of health and care, upskilling is also crucial when adapting in times of change [5, 6] or crisis [7] and to align with up-to-date best practice.

Health and care providers may range from registered clinicians such as surgeons, general practitioners and doctors, nurses and midwives, to allied health and non-registered staff who provide care. Allied health staff may include paramedics, dieticians, podiatrists and radiographers[8], while carers also

include those working for care-based organisations such as in care homes or homecare agencies.

Regardless of the role, all staff that provide health and care services must act in accordance with

policies/guidelines and optimally engage in up-to-date evidence-based best practice.

Evidence-based practice is widely recognised as the gold standard when providing effective and safe healthcare[9]. This requires professionals to update and upskill themselves on current evidence and to alter their practice to align with this, as well as with their patient's preferences[10]. Current evidence is usually retrieved from peer-reviewed journal articles; however, due to time constraints and workload demand, many health and care staff rely on organisational policies and protocols as formal sources of knowledge[11]. As the evidence base grows, old habits must be adapted and upskilling is required to align with the newest best practice.

Upskilling is also essential when adapting in times of change or crisis. For example, the emergence of medical and healthcare technologies requires staff to upskill, including improving their digital literacy skills[5, 6]. Additionally, the novel coronavirus disease-19 (COVID-19) pandemic caused significant changes to health and care systems. Changes included staff deployment to wards (e.g. COVID-19 wards) outside of their normal experience and of retired and newly qualified staff, remote provision of healthcare using telehealth (phones, video, patient portals), distancing/minimal contact care, stringent use of personal protective equipment and strengthened inter-professional collaboration[12-15]. These challenges required prompt upskilling, especially in using technologies and in infection, prevention and control behaviours to minimise the spread of COVID-19.

Upskilling training programmes

Upskilling training programmes traditionally consist of e-learning, textbooks, workshops, seminars, shadowing/observation and reading peer-reviewed journal articles. Hatfield et al.[16] systematically reviewed 12 studies that delivered behaviour change training interventions to healthcare professionals. All used educational elements (e.g. presentations and workshops) and most were delivered in-person. Morris et al.[17] reviewed training interventions aimed at carers. Both reviews concluded that interventions that use both educational and practical elements (e.g. practising skills or discussion) are

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most effective [16, 17]. This indicates that education-only interventions may not be effective in upskilling health and care staff.

Time, organisational structure, difficult to access resources and a reliance on experiential knowledge also constrain providers from upskilling[3, 11]. Health and care staff have widely reported a preference for learning through 'doing' (such as interacting with or observing colleagues), rather than from journal articles or textbooks[18-20]. Additionally, although support and care workers provide clinical, care-based and clerical patient care, their value is often not reflected in their allocated training budgets and available programmes[3]. As a result, many feel insufficiently prepared[3]. However, clinical, health support and care staff indicate a willingness to upskill, receive further training and to participate in interventions that will improve their practice[11, 21]. Further, some managers and nurses in England-based nursing homes have expressed enthusiasm toward implementing innovative digital health technologies that may improve residents' quality of care[22].

Digital technologies for upskilling

Effective interventions that are short, accessible, interactive, memorable and low cost are needed, to overcome training barriers. For workplaces with staff shortages, training also needs to be flexible and provided on a drop-by basis[3]. Brief interventions delivered via digital technology may be appropriate, as they can be made available online and accessed 24/7. They can also be more engaging and memorable, by including interactive activities (e.g. games, quizzes, simulations and immediate performance feedback). However, there is limited literature on implementation strategies for digital interventions that upskill health and care workers. Theories of change can be applied to knowledge of existing barriers and facilitators to using digital health programmes for healthcare workers. Lewin describes behaviour as "a dynamic balance of forces working in opposing directions" [23]. Lewin theorises that driving forces (i.e. facilitators) and restraining forces (i.e. barriers) counter one another, but can result in change if one overrides the other. This means that barriers and facilitators directly impact the implementation success and effectiveness of digital training programmes for health and care staff.

Literature on digital health technologies has highlighted various driving and restraining forces that impact both implementation and the effectiveness of programmes. Keyworth et al.[24] conducted a review of 69 studies to determine what maximises the effectiveness and implementation of technology-based interventions that support healthcare professional practice. They concluded that successful technologies employ behaviour change theories and specific instruction on how to perform behaviours. They also provide professionals with knowledge and person-specific information to assist with practice (e.g. patient management). Driving forces for implementation include integration into clinical workload, alignment with organisational strategies and senior peer endorsement. Restraining forces include organisational challenges, as well as the design, content and technical issues of the interventions.

Literature also highlights key strategies for implementation, focussing on provider adoption and acceptance. Recommendations for facilitating change include linking new practice with old practice to build familiarity[25, 26], identifying people who are willing to facilitate and promote the new practice [26, 27] and to clearly communicate to staff as to how the new practice will benefit them and their patients [26, 28, 29]. Spagnoletti et al. [28] provide specific examples, highlighting that short sessions, role-modelling content (e.g. video clips of the behaviour) and modules that refresh

understanding of familiar curriculum were important in their implementation of an online training programme for interns.

Simulation technologies for upskilling

The implementation of simulation technologies may be a novel and engaging approach to upskilling health and care workers. Simulation in this context refers to the replication of real-life interactions or scenarios, whereby learners receive immediate feedback/de-briefing[30]. Various levels of simulation exist, depending on 'fidelity' (reality). According to Seropian et al.[31], these can be categorised as high, medium and low fidelity and use tools such as human-like body parts, haptic feedback, computer programmes (e.g. serious games) or virtual reality (VR) headsets to facilitate experimental learning. Low fidelity simulation may include a simple body part, such as a doll-like arm to practice intravenous insertion skills[32]. In contrast, high fidelity simulation tools include real-life responses driven by computers[32]. These are more expensive and may include the METI Human Patient Simulator, which looks and acts like a human (e.g. blinks, has a pulse and speaks) and accurately mirrors responses to clinical procedures, such as intubation and catheterisation. However, it is important to note that simulators mimic, rather than replicate reality[32].

Simulation technology has been found to be as effective as traditional teaching methods for educating health and care staff and students[33-35]. However, when compared to traditional methods, students report better retention of knowledge[36] and higher satisfaction and motivation when using simulation technologies such as games[34]. Experimental learning by simulation also allows for learners to repeatedly practice skills and make and learn from their mistakes without harming a patient, distressing them or facing other negative consequences[32, 37]. Computer-driven simulation technologies such as games, augmentation and VR also enable independent learning, without the need for an instructor to provide feedback or de-brief learners.

In VR, users wear a headset to become immersed in a digital environment. Headsets range from the low-cost Samsung Gear VR or Google Cardboard to high-end gaming equipment such as Oculus Touch. The extent of immersion also differs, ranging from non-immersion (e.g. using computer-based VR), semi-immersion and fully immersive simulations (e.g. those with haptic feedback). The perception of being immersed within a non-physical world is created through various stimuli, including images and sound[38], which enable users to learn from experience. In interactive medical VR, users can engage in virtual worlds, including with patients, colleagues and react to specific scenarios[30]. In contrast, within augmented reality (AR) real-world environments are complemented with interactive computer-generated imagery and information.

Unlike traditional simulators, the main benefit of VR is transporting the learner into an immersive environment, rather than an educational one. VR and AR interventions are also cost-effective as they can be used autonomously, independently, and repeatedly, compared to traditional simulation technologies. In fact, they have been deemed as the learning tool of the 21st century[39] and their popularity is expected to continually increase. Current projections for the AR/VR head-mounted display market include a worth of USD 25 billion by 2022, with an annual growth rate of 39.5%[40]. This highlights that now is the ideal time to research implementation of AR/VR, due to an inevitable growth in use and further reduction in costs.

These technologies have transformed clinical training and have been used to support health care workers in decision-making and teaching emergency response, resuscitation, robotic surgery and Page 7 of 23

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alcohol screening skills[41-45]. However, their effectiveness is contested within the literature, with some research stating that VR is not as effective as other training tools, including for phlebotomy training[46]. Other literature highlights that VR is useful for 'presence', but does not improve learning outcomes[47, 48]. It is hypothesised that VR increases cognitive load and therefore compromises cognitive resources from the learning experience[47]. Conversely, some research has found VR to be more effective than other educational techniques [49, 50], with systematic reviews concluding that VR training is effective in improving technical skills for arthroscopic surgery [51] and knowledge and skill performance when learning clinical psychomotor skills[52]. Evidently, research is needed to explore to what extent and for whom VR interventions are effective.

Despite their contested effectiveness, VR and AR technologies have now been commercialised and implemented to upskill and support health providers. FundamentalVR[53], for example, provides flight simulator-like training for surgeons with the use of haptic elements for tactile feedback. In the SentiAR[54] tool, holographic visualisations are provided for each patients anatomy and float alongside or above the patient during procedures (e.g. treating cardiac arrhythmias). Other tools include the AR xVision[55] three-dimensional anatomical images that enable clinical providers to see a patient's skin and tissue (akin to x-ray vision) and the AR SureWash[56] mobile app, which provides personalised feedback for hand hygiene technique. VR technologies were also implemented during the COVID-19 pandemic when face-to-face teaching was not possible[57]. For example, St Bartholomew's Hospital used VR to train their nurses and doctors on 50 clinical procedures[58]. Their OMS VR system provided performance feedback, tracked improvement and facilitated group learning.

Gap in research and aim

Despite the emergence and potential effectiveness of simulation technologies, there is an absence of research on their effectiveness as an educational intervention. This includes how good they are at enabling upskilling compared to other strategies, and how they can be implemented into a practice setting, to enable upskilling. Additionally, as evident in the mixed findings on the effectiveness of AR and VR interventions in upskilling staff, programme interventions, including digital ones, do not work for everyone equally[59]. A gap in research remains on the factors that influence when an AR or VR intervention works, to what extent, for whom and in which context. Moreover, research is needed on the causal mechanisms that influence the outcomes of AR/VR interventions and their implementation. This is essential in ensuring that future digital interventions are designed and appropriately targeted at health and care workers, for both maximum efficiency and sustained effects. The aim of this review is to develop, test and refine an evidence-informed programme theory on what facilitates or constrains the implementation of AR or VR programmes in health and care settings and understand how, for whom and to what extent they 'work.'

METHODS AND ANALYSIS

Realist review

This research will take a realist approach because it can produce useful answers to complex questions often left unexplored by experimental research [59]. These questions include: how, when, for whom and to what extent, does an intervention 'work'? To answer these questions, realist approaches consider the complex interactions between the environment, individuals and the intervention.

1

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2		
2	1	Realist evaluation is an emerging theory-driven methodology that seeks to understand CMO
4	2	configurations, i.e. the context (C), mechanisms (M) and outcomes (O) of interventions. Context
5	2	refers to the backdrop of conditions that may impact outcomes, such as organisational structure,
6		
7	4	environmental settings, culture and norms. These trigger or modify mechanisms (causal forces) that
8 9	5	influence outcomes[60]. Examples of mechanisms include the resources offered by interventions or
9 10	6	changes in reasoning or behaviour.
11	7	
12	8	Realist reviews seek to understand context, mechanisms and outcomes, by identifying candidate
13	9	theories and then systematically reviewing literature for underlying social entities, processes or social
14	10	structures that result in the intended outcome[61]; rather than assuming that the intervention itself
15	11	produces an outcome. This process is useful for complex interventions, in which outcomes may not
16 17	12	necessarily be linear, and instead depend on the context and both intended and unintentional
18	13	mechanisms[61]. It also allows exploring how an intervention is meant to work compared to how it
19	14	actually works in practice[62]. Additionally, 'demi-regularities' are identified to acknowledge that
20	15	outcomes will vary across contexts, but some CMO patterns will remain[60]. This focuses reviewers
21	16	on the transferable aspects of a programme theory[61].
22	17	
23	17	CMO configurations are then developed as a programme theory, which is tested and refined in real-
24 25	10 19	
25 26		life settings and with key stakeholders[59]. As with AR/VR technologies, the main benefit of realist
27	20	evaluation is the ability to bridge theory and practical application in the contexts and with the
28	21	populations that the intervention targets[59].
29	22	
30	23	A realist review will therefore help to answer the following questions:
31	24	• What facilitates or constrains the implementation of AR/VR programmes in health and care
32 33	25	settings?
34	26	• What are the mechanisms by which VR/AR interventions result in their intended outcomes?
35	27	• What contexts determine whether the different mechanisms produce their intended outcomes?
36	28	• In what circumstances and for whom are VR/AR interventions effective in upskilling health
37	29	and care providers?
38	30	
39 40	31	The core research team is a multi-disciplinary group of researchers, from the backgrounds of nursing,
40 41	32	primary healthcare, health informatics and implementation. Across this group, expertise relevant to
42	33	the topic includes that on digital health innovation and evaluation, behaviour change, implementation
43		
44	34	science and conducting realist reviews. The RAMESES training documents[61] will be referred to,
45	35	and the review will be reported in accordance with the RAMESES Publication Standards for Realist
46	36	Synthesis[63] (supplementary Table S1).
47 48	37	
40 49	38	Procedures
50	39	
51	40	Realist reviews tend to follow a three-step process: theory elicitation, theory testing, and theory
52	41	refinement. This process will be followed to describe our procedures. Unlike systematic reviews,
53	42	which aim to uncover all research relevant to the topic, realist reviews find a comprehensive balance
54 57	43	of empirical research and theory[64]. Searches will therefore be iterative and additional rounds of
55 56	44	searching may alter the following procedures. Figure 1 highlights the processes that will be conducted
50 57	45	in each stage.
58	46	
59	47	
60	- '	

1. Theory elicitation	
Search strategy	
A search will be conducted to identify initial candi	-
publication date and are characterised as academic	, practitioner and learning and technology adopti
theories.	
We will identify academic and practitioner theorie	a voing free tout and MaSII terms when seerchin
Medline, SCOPUS, CINAHL, EMBASE, Education	
Web of Science. Snowballing will also help to iden	
provides the search strategy. An initial search of the	
which 200 were deemed potentially eligible, after	
which 200 were deemed potentially engible, after	reviewing their titles and abstracts.
We will focus on the discussion section of items, t	o identify why AR or VR interventions did or di
not achieve their intended outcomes. These often i	
systematic reviews will first be reviewed.	nerude the duthor's theories[05]. Existing
systematic reviews will first be reviewed.	
Relevant practitioner theories may be presented by	professional bodies, or within grey literature.
P	
including editorials, letters, news articles and com	mentaries[66]. We will therefore supplement the
including editorials, letters, news articles and comp above search with the additional journals presented Table 1. Summary of relevant journals related to c	d in Table 1.
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3 4		Journal of Nursing Education and Practice
5 6		Nurse Education Today
7 8		International Journal of Nursing Studies
9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	1 2 3 4 5 6 7 8 9 10 11 12	 We will also identify theories related to adult learning from the academic articles. These are expected to include theories related to adult learning for health and care professionals, including the Schon[67] theory on the reflective practitioner, and Slotnick's[68] theory on how physicians learn. Two theories identified by Mukhalalati and Taylor[69] as key to professional learning are directly applicable to AR/VR. These include: Experiential learning, whereby knowledge construction and learning are facilitated through interaction with the environment. Kolb[70] proposes a framework for experiential learning that includes concrete experience, reflective observation, abstract conceptualisation, and active experimentation.
24	13	• In constructivism, learning occurs through interaction between previous skills/knowledge,
25 26	14	those gained through social interaction and social activities, within the learner's environment,
27	15	physical and social world[71]. Simulation has been identified as a tool that supports
28 29	16 17	constructive learning[72, 73], as constructivists generally believe that people learn best by 'doing ' as this is how they construct their knowledge[74]
30	17	'doing,' as this is how they construct their knowledge[74].
31	10	Theories may also relate to technology acceptance and adoption. Frameworks include:
32 33	20	• The Diffusion of Innovations theory[75], which explains how and at what rate innovations
34	21	(e.g. technologies) spread, as determined by different categories of adopters. This can be
35 36	22	applied to organisations and individuals.
37	23	• The Technology Acceptance Model[76] explains that an individual's perceived usefulness
38	24	and ease–of-use of a technology influence intention to use and actual use.
39 40	25	• The Unified Theory of Acceptance and Use of Technology[77] determines that four
41	26 27	constructs: performance expectancy, effort expectancy; social influence; and, facilitating conditions (e.g. age, gender, experience and voluntariness of use) influence an individual's
42	28	technology use and acceptance.
43 44	29	 The NASSS framework[78] evaluates reasons for non-adoption, abandonment, and
45	30	challenges to implementation through six domains (condition, technology, value proposition,
46	31	adopter system and institutional and societal contexts).
47 48	32	• The Consolidated Framework for Implementation Research[79] considers five domains
40	33	related to the intervention, outer and inner settings, the individuals involved and
50	34 25	implementation process.
51 52	35 36	• The Normalisation Process Theory[80] focuses on people's actions, rather than their intentions/beliefs. It considers coherence, cognitive participation, collective action and
52	37	reflexive monitoring as crucial to the implementation process.
54	38	
55	39	Record management
56 57	40	
58	41	Similar to the methods in Randell et al.[62], records will be saved to an Endnote library, as well as
59	42 43	charted on Excel. A timeline sheet on Excel will record search activities, including the databases
60	43	searched, the date of each search and the number of records found.

BMJ Open

1		
2 3		
3 4	1	
5	2	Screening
6	3	
7	4	Two researchers (NG and DD) will screen the literature for eligibility, starting by determining the
8	5	relevance from the title and abstract, and then reading the full-text. The inclusion criteria for the
9	6	academic and practitioner theories will be:
10		
11	7	• Using simulation technologies (any type of immersion will be accepted)
12	8	 Health and care workers and individuals post-graduation/registration as learners.
13	9	• Any health, care or university-based setting (as these often have simulation labs)
14	10	• Includes detail on implementation and/or on what contexts, how and for whom they 'worked.'
15	11	• Published in English
16	12	
17 18		
10	13	The exclusion criteria include simulation technologies that do not use augmentation or VR (e.g. low
20	14	fidelity web-based e-learning interventions or manikin-only simulators), undergraduate students and
21	15	published in languages other than English. Work also including undergraduate learners or other
22	16	simulation technologies will only be included if the data for post-graduate/registered learners and
23	17	AR/VR can be separated.
24	18	
25	19	A PRISMA flowchart[81] will document the review selection and decision process.
26	20	A l'how in a counter a counter a constant and a constant process.
27		
28	21	Analysis and synthesis
29	22	
30 31	23	We will extract relevant information (presented in Box 1) including that pertaining to context,
32	24	mechanism and outcomes from each article from the academic and practitioner theories. Adult
33	25	learning and technology adoption theories will be briefly summarised. For consistency, outcomes
34	26	should broadly be related to the Kirkpatrick et al. [82] components of evaluation: reaction (i.e.
35	27	satisfaction), learning (i.e. knowledge), behaviour or results (skills). Unintended and other subjective
36	28	or observed outcomes (e.g. increased confidence or perceived interactivity) will be included too. A
37	29	second reviewer will code and extract data from a random selection of 10-20% of the articles to
38	30	
39		ensure consistency in interpretation.
40	31	
41 42	32	All information will be recorded in an Excel sheet for analysis. If possible, complete CMO
43	33	configurations will be recorded, however; it is unlikely that all articles will contain complete
44	34	statements- fragments will therefore be recorded too[62].
45	35	
46	36	Upon completion, we will conduct a narrative synthesis to determine any overlapping CMO
47	37	configurations. These will then be compared with identified (learning and adoption) theories to further
48	38	explore the underlying causal mechanisms so as to understand how VR/AR interventions can or
49	39	should upskill health and care professionals[83]. The resulting CMO configurations will answer (a)
50		
51	40	what facilitates or constrains the implementation of AR/VR programmes in health and care settings?
52	41	(b) How, for whom and to what extent did they produce the intended outcomes (reaction/satisfaction,
53 54	42	learning/knowledge and behaviour/results)?
54 55	43	
56	44	The research team will then select a number of CMO configurations to test, focusing on those that are
57	45	most feasible and likely to apply to future AR or VR interventions.
58	46	
59	47	2. Theory testing
60	1/	z. incory wounds

2 <u>Search strategy</u>

We will search databases to identify empirical and published studies that will enable the CMO configurations to be tested. We will use the same databases and keywords as in step one. Snowballing will help to identify additional literature.

8 <u>Screening</u>

10 The articles will be screened by determining their relevance to the programme theory (e.g. AR/VR 11 tools used by health and care workers). A benefit of realist reviews is the focus on the intervention 12 mechanism, enabling the inclusion of literature whereby the intervention has been applied to different 13 settings, people or even similar interventions in the same setting[66, 84]. All study designs will be 14 included. A PRISMA diagram will visualise the study selection process[81].

16 <u>Analysis and synthesis</u>

Relevant information (presented in Box 1) will be extracted into an excel sheet. We will also assess the quality of each paper using the Mixed Methods Appraisal Tool (MMAT), as this is appropriate for qualitative, quantitative and mixed methods research[85]. The MMAT was developed in 2007[86], and revised in 2011[87]. Unlike earlier versions, the newest 2018 MMAT is not intended to be quantified and instead offers a guide for discussing quality. We will therefore highlight methodological flaws to inform recommendations for future research. Low quality research will not be excluded, as realist methodologists acknowledge that useful information on contextual factors may be present[88]. In alignment with the guidelines for conducting realist reviews, the quality of each study will focus on the evidential fragment (relevant section) that each theory is drawn from[88]. For example, when only quantitative data is used from a mixed-methods study to test the theory, the quality of the qualitative component will not be assessed.

30 3. Theory refinement

32 Coded data will be compared to the initial programme theory, and differences will be identified to 33 refine and revise the programme theory. Upon completion of the final theory, a narrative and 34 diagrammatic summary will be presented[89, 90]. We will use the MMAT to assess the extent to 35 which we are confident in each finding. Ultimately, each CMO configuration will be rated as high, 36 moderate, low or very low in confidence. This rating will highlight areas for research and also support 37 decision-makers when deciding whether to implement or develop similar technologies to upskill 38 health and care workers.

40 Patient and public involvement

42 Members of the public were not involved in the development of this protocol.

44 ETHICS, DISSEMINATION AND CONCLUSION

46 Ethics approval is not required to conduct this realist review. This protocol describes how we will
 47 conduct a realist review that constructs, tests and refines an evidence-informed programme theory on
 48 what facilitates or constrains the implementation of AR/VR programmes in health and care settings

1		
2		
3	1	and how, for whom and to what extent they 'work.' The results may inform and support AR/VR
4	2	interventions from clinical educators, healthcare providers and software developers. Upskilling
5 6	3	through AR/VR learning interventions may ultimately improve quality of care and promote evidence-
0 7	4	based practice and continued learning. Findings will be disseminated through conference
8	5	
9		presentations and peer-reviewed journal publications.
10	6	
11	7	AUTHOR CONTRIBUTIONS
12	8	
13	9	NG conceived and designed the study with support from DD, SNVDV and PW. NG wrote the first
14	10	draft of the manuscript. All authors revised and approved the final manuscript.
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17	13	Tending
18 10		This much is finded here the Netional Institute for Health Descende Analised Descende Calleboardian
19 20	14	This work is funded by the National Institute for Health Research Applied Research Collaboration
20	15	Greater Manchester. The views expressed in this publication are those of the authors and not
22	16	necessarily those of the National Institute for Health Research or the Department of Health and Social
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24	18	
25	19	COMPETING INTERESTS
26	20	
27	21	The authors have no competing interests to declare.
28		The authors have no competing interests to declare.
29	22	
30	23	PATIENT CONSENT FOR PUBLICATION
31	24	
32	24 25	Not required.
32 33		Not required.
32 33 34	25	Not required. REFERENCES
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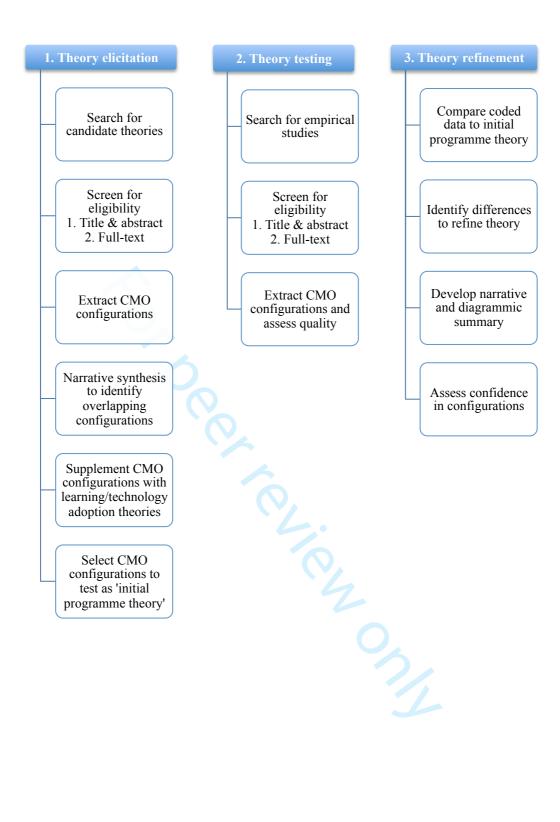
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36	31	Figure 1. Summary of the three steps and process that will be conducted. CMO stands for Context
37	32	Mechanism and Outcome.
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		Day 1. Contant to be systemated from included sources and recorded in the solding sheet
40	34	Box 1. Content to be extracted from included sources and recorded in the coding sheet
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Research design, theoretical orientation (if

Outcome (intended, unintended and/or subjective)

Implementation (strategy, adoption and/or uptake)

Learning or technology adoption theories

Author; date

Type of publication

applicable) and methods

Study objective (focus)

Setting; country

Context

Mechanism

mentioned

AR/VR technology description

Sample (type, size, age, gender)

Title

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Supplementary file

Table S1. Completed checklist of the RAMESES Publication Standards for realist reviews¹

No.			Rep	Reported	
			Yes	N/A	
Title		· · · · · · · · · · · · · · · · · · ·			
1.		In the title, identify the document as a realist synthesis or	Х		
		review.			
Abst	ract				
2.		While acknowledging publication requirements and	Х		
		house style, abstracts should ideally contain brief details			
		of: the study's background, review question or			
		objectives; search strategy; methods of selection,			
		appraisal, analysis and synthesis of sources; main			
		results; and implications for practice			
	duction				
3.	Rationale for	Explain why the review is needed and what it is likely to	Х		
	review	contribute to existing understanding of the topic area.			
4.	Objectives	State the objective(s) of the review and/or the review	Х		
	and focus of	question(s). Define and provide a rationale for the focus			
	review	of the review.			
Meth					
5.	Changes in	Any changes made to the review process that was		Х	
	the review	initially planned should be briefly described and			
(process	justified.	V		
6.	Rationale for	Explain why realist synthesis was considered the most	Х		
	using realist	appropriate method to use.			
7.	synthesis	Describe and justify the initial process of surlenstary	v		
1.	Scoping the literature	Describe and justify the initial process of exploratory	Х		
8.	Searching	scoping of the literature. While considering specific requirements of the journal	X		
0.	e	or other publication outlet, state and provide a rationale	Λ		
	processes	for how the iterative searching was done. Provide details			
		on all the sources accessed for information in the review.			
		Where searching in electronic databases has taken place,			
		the details should include, for example, name of			
		database, search terms, dates of coverage and date last			
		searched. If individuals familiar with the relevant			
		literature and/or topic area were contacted, indicate how			
		they were identified and selected.			
9.	Selection and	Explain how judgements were made about including and	Х		
	appraisal of	excluding data from documents, and justify these.			
	documents				
10.	Data	Describe and explain which data or information were	Х		
	extraction	extracted from the included documents and justify this			

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		selection.		
11.	Analysis and	Describe the analysis and synthesis processes in detail.	Х	
	synthesis	This section should include information on the		
	processes	constructs analysed and describe the analytic process.		
Resu	lts			•
12.	Document	Provide details on the number of documents assessed for		Х
	flow diagram	eligibility and included in the review with reasons for		
		exclusion at each stage as well as an indication of their		
		source of origin (for example, from searching databases,		
		reference lists and so on). You may consider using the		
		example templates (which are likely to need		
		modification to suit the data) that are provided.		
13.	Document	Provide information on the characteristics of the		Х
	characteristic	documents included in the review.		
	s			
14.	Main	Present the key findings with a specific focus on theory		Х
	findings	building and testing.		
Discu	ission			
15.	Summary of	Summarise the main findings, taking into account the		X
	findings	review's objective(s), research question(s), focus and		
	_	intended audience(s).		
16.	Strengths,	Discuss both the strengths of the review and its		Х
	limitations	limitations. These should include (but need not be		
	and future	restricted to) (a) consideration of all the steps in the		
	research	review process and (b) comment on the overall strength		
	directions	of evidence supporting the explanatory insights which		
		emerged.		
		The limitations identified may point to areas where		
		further work is needed.		
17.	Comparison	Where applicable, compare and contrast the review's		Х
	with existing	findings with the existing literature (for example, other		
	literature	reviews) on the same topic.		
18.	Conclusion	List the main implications of the findings and place		Х
	and	these in the context of other relevant literature. If		
	recommendat	appropriate, offer recommendations for policy and		
	ions	practice.		
19.	Funding	Provide details of funding source (if any) for the review,	Х	
	_	the role played by the funder (if any) and any conflicts		
		of interests of the reviewers.		

¹Wong, G., Greenhalgh, T., Westhorp, G., et al. RAMESES publication standards: realist syntheses. *BMC Medicine* 2013;11(1):21.

Table S2. Initial search strategy

Databases	
	Medline
	SCOPUS
	CINAHL
	EMBASE
	Education Resource Information Centre
	PsycINFO
7	Web of Science
Keywords	- · · · · · · · · · · · · · · · · · · ·
Technology/Intervention	augmented reality
	• virtual reality
	1 114
Population/sample	• health*
	healthcare; health; health worker; health staff; health provider
	• care*
	care; carer; caregiving; caregiver; caring
	• nurs*
	nurse, nursing, nurses
	doctor
	• surgeon
Focus	• training
	upskilling
	• skill
	• education
	• evaluation
	implementation
	• feasibility
	 effectiveness
Example with Boolean operators	
	(TITLE-ABS-KEY (augmented AND reality
	OR virtual AND reality) AND TITLE-ABS-
	KEY (health* OR care* OR nurs* OR doct
	OR surgeon) AND TITLE-ABS-KEY (
	training OR upskilling OR skill OR education
) AND TITLE-ABS-KEY (evaluation OR
	implementation OR feasibility OR
	effectiveness))

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Table S1. Completed checklist of the RAMESES Publication Standards for realist reviews¹

No.	Section /	Checklist item	Reported	
	Торіс		Yes	N/A
Title				
1.		In the title, identify the document as a realist synthesis or	Х	
		review.		
Abstr	act			
2.		While acknowledging publication requirements and	Х	
		house style, abstracts should ideally contain brief details		
		of: the study's background, review question or		
		objectives; search strategy; methods of selection,		
		appraisal, analysis and synthesis of sources; main		
		results; and implications for practice		
Intro	duction			
3.	Rationale for	Explain why the review is needed and what it is likely to	Х	
	review	contribute to existing understanding of the topic area.		
4.	Objectives	State the objective(s) of the review and/or the review	Х	
	and focus of	question(s). Define and provide a rationale for the focus		
	review	of the review.		
Meth	ods			
5.	Changes in	Any changes made to the review process that was		X
	the review	initially planned should be briefly described and		
	process	justified.		
6.	Rationale for	Explain why realist synthesis was considered the most	Х	
	using realist	appropriate method to use.		
	synthesis			
7.	Scoping the	Describe and justify the initial process of exploratory	Х	
	literature	scoping of the literature.		
8.	Searching	While considering specific requirements of the journal	Х	
	processes	or other publication outlet, state and provide a rationale		
		for how the iterative searching was done. Provide details		
		on all the sources accessed for information in the review.		
		Where searching in electronic databases has taken place,		
		the details should include, for example, name of		
		database, search terms, dates of coverage and date last		
		searched. If individuals familiar with the relevant		
		literature and/or topic area were contacted, indicate how		
		they were identified and selected.		
9.	Selection and	Explain how judgements were made about including and	Х	
	appraisal of	excluding data from documents, and justify these.		
	documents			
10.	Data	Describe and explain which data or information were	X	
	extraction	extracted from the included documents and justify this	-	
		selection.		

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11.	Analysis and synthesis	Describe the analysis and synthesis processes in detail. This section should include information on the	Х	
	processes	constructs analysed and describe the analytic process.		
Result				37
12.	Document flow diagram	Provide details on the number of documents assessed for eligibility and included in the review with reasons for exclusion at each stage as well as an indication of their source of origin (for example, from searching databases, reference lists and so on). You may consider using the example templates (which are likely to need modification to suit the data) that are provided.		Х
13.	Document	Provide information on the characteristics of the		Х
	characteristic	documents included in the review.		
	S			
14.	Main	Present the key findings with a specific focus on theory		Х
	findings	building and testing.		
Discus	ssion		1	
15.	Summary of	Summarise the main findings, taking into account the		Х
	findings	review's objective(s), research question(s), focus and		
		intended audience(s).		
16.	Strengths,	Discuss both the strengths of the review and its		Х
	limitations	limitations. These should include (but need not be		
	and future	restricted to) (a) consideration of all the steps in the		
	research	review process and (b) comment on the overall strength		
	directions	of evidence supporting the explanatory insights which		
		emerged.		
		The limitations identified may point to areas where		
		further work is needed.		
17.	Comparison	Where applicable, compare and contrast the review's		Х
	with existing	findings with the existing literature (for example, other		
	literature	reviews) on the same topic.		
18.	Conclusion	List the main implications of the findings and place		Х
	and	these in the context of other relevant literature. If		
	recommendat	appropriate, offer recommendations for policy and		
	ions	practice.		
19.	Funding	Provide details of funding source (if any) for the review,	X	
		the role played by the funder (if any) and any conflicts		
		of interests of the reviewers.		

¹Wong, G., Greenhalgh, T., Westhorp, G., et al. RAMESES publication standards: realist syntheses. *BMC Medicine* 2013;11(1):21.

Upskilling health and care workers with augmented and virtual reality: Protocol for a realist review to develop an evidence-informed programme theory

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4	1	ABSTRACT
5	2	
6	3	Introduction
7	4	Augmented reality (AR) and virtual reality (VR) are increasingly used to upskill health and care
8	5	providers, including in surgical, nursing and acute care settings. Many studies have used AR/VR to
9 10	6	deliver training, providing mixed evidence on their effectiveness and limited evidence regarding
10	7	contextual factors that influence effectiveness and implementation. This review will develop, test and
12	8	refine an evidence-informed programme theory on what facilitates or constrains the implementation
13	9	of AR or VR programmes in health and care settings and understand how, for whom and to what
14	10	extent they 'work.'
15	11	
16	12	Method and analysis
17 18	13	This realist review adheres to the RAMESES standards and will be conducted in three steps: theory
19	14	elicitation, theory testing, and theory refinement. First, a search will identify practitioner, academic
20	15	and learning and technology adoption theories from databases (Medline, SCOPUS, CINAHL,
21	16	EMBASE, Education Resource Information Centre, PsycINFO and Web of Science), practitioner
22	17	journals, snowballing and grey literature. Information regarding context, mechanism and outcome will
23		
24 25	18	be extracted. A narrative synthesis will determine overlapping configurations and form an initial
25 26	19	theory. Second, the theory will be tested using empirical evidence located from the above databases
27	20	and identified from the first search. Quality will be assessed using the Mixed Methods Appraisal Tool
28	21	(MMAT), and relevant information will be extracted into a coding sheet. Third, the extracted
29	22	information will be compared to the initial programme theory, with differences helping to make
30	23	refinements. Findings will be presented as a narrative summary, and the MMAT will determine our
31	24	confidence in each configuration.
32 33	25	
34	26	Ethics and dissemination
35	27	Ethics approval is not required. This review will develop an evidence-informed programme theory.
36	28	The results will inform and support AR/VR interventions from clinical educators, healthcare
37	29	providers and software developers. Upskilling through AR/VR learning interventions may improve
38	30	quality of care and promote evidence-based practice and continued learning. Findings will be
39 40	31	disseminated through conference presentations and peer-reviewed journal articles.
40	32	
42	33	KEYWORDS
43	34	healthcare; learning; simulation; virtual reality; augmented reality; realist review
44	35	
45	36	STRENGTHS AND LIMITATIONS OF THIS STUDY
46 47	37	• Including quality assessments and identifying our confidence in each CMO configuration will
48	38	improve applicability of the programme theory.
49		
50	39	• The repeated search will help to include recently published and up-to-date literature.
51	40	• This review will be conducted systematically, which enhances reproducibility.
52	41	• The literature review may be subject to selection bias, because it will only include published,
53 54	42	peer-reviewed studies in English.
54 55	43	• The mechanisms extracted will likely be untested and subjective author hypotheses.
56	44	
57	45	WORD COUNT: 4,397
58	46	
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INTRODUCTION

Upskilling in the health and care workforce

Upskilling through continuous learning and development is important in any business, to improve skillsets, advance practice and close gaps in knowledge. Upskilling is the process of learning new skills or refining existing skillsets to enable employees to continue practising with ease[1]. For health support and care workers, upskilling ensures that their work is safe and aligns with best practice guidelines, as they often receive variable and inconsistent training, as non-registered staff[2,3]. Upskilling, in this sense, is therefore essential for providing consistent and high-quality care. Additionally, this promotes workforce flexibility and enables for the delegation of skills, when systems experience a shortage of staff[4]. Within the provision of health and care, upskilling is also crucial when adapting in times of change [5,6] or crisis [7] and to align with up-to-date best practice.

Health and care providers may range from registered clinicians such as surgeons, general practitioners and doctors, nurses and midwives, to allied health and non-registered staff who provide care. Allied health staff may include paramedics, dieticians, podiatrists and radiographers[8], while carers also include those working for care-based organisations such as in care homes or homecare agencies. Regardless of the role, all staff that provide health and care services must act in accordance with policies/guidelines and optimally engage in up-to-date evidence-based best practice.

Evidence-based practice is widely recognised as the gold standard when providing effective and safe healthcare[9]. This requires professionals to update and upskill themselves on current evidence and to alter their practice to align with this, as well as with their patient's preferences[10]. Current evidence is usually retrieved from peer-reviewed journal articles; however, due to time constraints and workload demand, many health and care staff rely on organisational policies and protocols as formal sources of knowledge[11]. As the evidence base grows, old habits must be adapted and upskilling is required to align with the newest best practice.

Upskilling is also essential when adapting in times of change or crisis. For example, the emergence of medical and healthcare technologies requires staff to upskill, including improving their digital literacy skills[5,6]. Additionally, the novel coronavirus disease-19 (COVID-19) pandemic caused significant changes to health and care systems. Changes included staff deployment to wards (e.g. COVID-19 wards) outside of their normal experience and of retired and newly qualified staff, remote provision of healthcare using telehealth (phones, video, patient portals), distancing/minimal contact care, stringent use of personal protective equipment and strengthened inter-professional collaboration[12-15]. These challenges required prompt upskilling, especially in using technologies and in infection, prevention and control behaviours to minimise the spread of COVID-19.

Upskilling training programmes

Upskilling training programmes traditionally consist of e-learning, textbooks, workshops, seminars, shadowing/observation and reading peer-reviewed journal articles. Hatfield et al.[16] systematically reviewed 12 studies that delivered behaviour change training interventions to healthcare professionals. All used educational elements (e.g. presentations and workshops) and most were delivered in-person. Morris et al.[17] reviewed training interventions aimed at carers. Both reviews concluded that interventions that use both educational and practical elements (e.g. practising skills or discussion) are

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most effective [16,17]. This indicates that education-only interventions may not be effective in upskilling health and care staff.
Time, organisational structure, difficult to access resources and a reliance on experiential knowledge also constrain providers from upskilling[3,11]. Health and care staff have widely reported a preference for learning through 'doing' (such as interacting with or observing colleagues), rather that from journal articles or textbooks[18-20]. Additionally, although support and care workers provide clinical, care-based and clerical patient care, their value is often not reflected in their allocated training budgets and available programmes[3]. As a result, many feel insufficiently prepared[3]. However, clinical, health support and care staff indicate a willingness to upskill, receive further training and to participate in interventions that will improve their practice[11,21]. Further, some managers and nurses in England-based nursing homes have expressed enthusiasm toward implementing innovative digital health technologies that may improve residents' quality of care[22]
Digital technologies for upskilling
Effective interventions that are short, accessible, interactive, memorable and low cost are needed, to overcome training barriers. For workplaces with staff shortages, training also needs to be flexible ar provided on a drop-by basis[3]. Brief interventions delivered via digital technology may be appropriate, as they can be made available online and accessed 24/7. They can also be more engagin and memorable, by including interactive activities (e.g. games, quizzes, simulations and immediate performance feedback). However, there is limited literature on implementation strategies for digital interventions that upskill health and care workers. Theories of change can be applied to knowledge existing barriers and facilitators to using digital health programmes for healthcare workers. Lewin describes behaviour as "a dynamic balance of forces working in opposing directions" [23]. Lewin theorises that driving forces (i.e. facilitators) and restraining forces (i.e. barriers) counter one anothe but can result in change if one overrides the other. This means that barriers and facilitators directly impact the implementation success and effectiveness of digital training programmes for health and care staff.
Literature on digital health technologies has highlighted various driving and restraining forces that impact both implementation and the effectiveness of programmes. Keyworth et al.[24] conducted a review of 69 studies to determine what maximises the effectiveness and implementation of technology-based interventions that support healthcare professional practice. They concluded that successful technologies employ behaviour change theories and specific instruction on how to perfor behaviours. They also provide professionals with knowledge and person-specific information to ass with practice (e.g. patient management). Driving forces for implementation include integration into clinical workload, alignment with organisational strategies and senior peer endorsement. Restraining forces include organisational challenges, as well as the design, content and technical issues of the interventions.
Literature also highlights key strategies for implementation, focussing on provider adoption and acceptance. Recommendations for facilitating change include linking new practice with old practice to build familiarity[25,26], identifying people who are willing to facilitate and promote the new practice[26,27] and to clearly communicate to staff as to how the new practice will benefit them and their patients[26,28,29]. Spagnoletti et al.[28] provide specific examples, highlighting that short

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Literature lights key strategies for implementation, focussing on provider adoption and acceptanc nendations for facilitating change include linking new practice with old practice 44 to build f 25,26], identifying people who are willing to facilitate and promote the new 56 45 practice[2 to clearly communicate to staff as to how the new practice will benefit them and 57 46 their pati 29]. Spagnoletti et al. [28] provide specific examples, highlighting that short 58 47 59 sessions, role-modelling content (e.g. video clips of the behaviour) and modules that refresh 60

understanding of familiar curriculum were important in their implementation of an online training
 programme for interns.

Simulation technologies for upskilling

The implementation of simulation technologies may be a novel and engaging approach to upskilling health and care workers. The term health and care workers captures the breadth of professionals working in health and social care, including medical staff, general practitioners, nurses, carers and community workers. Simulation in this context refers to the replication of real-life interactions or scenarios, whereby learners receive immediate feedback/de-briefing[30]. Various levels of simulation exist, depending on 'fidelity' (reality). According to Seropian et al.[31], these can be categorised as high, medium and low fidelity and use tools such as human-like body parts, haptic feedback, computer programmes (e.g. serious games) or virtual reality (VR) headsets to facilitate experimental learning. Low fidelity simulation may include a simple body part, such as a doll-like arm to practice intravenous insertion skills[32]. In contrast, high fidelity simulation tools include real-life responses driven by computers[32]. These are more expensive and may include the METI Human Patient Simulator, which looks and acts like a human (e.g. blinks, has a pulse and speaks) and accurately mirrors responses to clinical procedures, such as intubation and catheterisation. However, it is important to note that simulators mimic, rather than replicate reality[32].

Simulation technology has been found to be as effective as traditional teaching methods for educating health and care staff and students [33-35]. However, when compared to traditional methods, students report better retention of knowledge[36] and higher satisfaction and motivation when using simulation technologies such as games[34]. Experimental learning by simulation also allows for learners to repeatedly practice skills and make and learn from their mistakes without harming a patient, distressing them or facing other negative consequences[32,37]. Computer-driven simulation technologies such as games, augmentation and VR also enable independent learning, often without the need for an instructor to immediately provide feedback or de-brief learners. De-briefing can then occur at a later date, such as to determine trainee performance and learning progress.

In VR, users wear a headset to become immersed in a digital environment. Headsets range from the low-cost Samsung Gear VR or Google Cardboard to high-end gaming equipment such as Oculus Touch. The extent of immersion also differs, ranging from non-immersion (e.g. using computer-based VR), semi-immersion and fully immersive simulations (e.g. those with haptic feedback). The perception of being immersed within a non-physical world is created through various stimuli, including images and sound[38], which enable users to learn from experience. In interactive medical VR, users can engage in virtual worlds, including with patients, colleagues and react to specific scenarios[30]. In contrast, within augmented reality (AR) real-world environments are complemented with interactive computer-generated imagery and information.

Unlike traditional simulators, the main benefit of VR is transporting the learner into an immersive environment. VR and AR interventions are also cost-effective as they can be used autonomously, independently, and repeatedly, compared to traditional simulation technologies. In fact, they have been deemed as the learning tool of the 21st century [39] and their popularity is expected to continually increase. Current projections for the AR/VR head-mounted display market include a worth of USD 25 billion by 2022, with an annual growth rate of 39.5%[40]. This highlights that now is the ideal time to research implementation of AR/VR, due to an inevitable growth in use and further reduction in costs.

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These technologies have transformed clinical training and have been used to support health care workers in decision-making and teaching emergency response, resuscitation, robotic surgery and alcohol screening skills[41-45]. However, their effectiveness is contested within the literature, with some research stating that VR is not as effective as other training tools, including for phlebotomy training[46]. Other literature highlights that VR is useful for 'presence', but does not improve learning outcomes[47,48]. It is hypothesised that VR increases cognitive load and therefore compromises cognitive resources from the learning experience [47]. Conversely, some research has found VR to be more effective than other educational techniques[49,50], with systematic reviews concluding that VR training is effective in improving technical skills for arthroscopic surgery[51] and knowledge and skill performance when learning clinical psychomotor skills[52]. Evidently, research is needed to explore to what extent and for whom VR interventions are effective. Despite their contested effectiveness, VR and AR technologies have now been commercialised and implemented to upskill and support health providers. FundamentalVR[53], for example, provides flight simulator-like training for surgeons with the use of haptic elements for tactile feedback. In the SentiAR[54] tool, holographic visualisations are provided for each patients anatomy and float alongside or above the patient during procedures (e.g. treating cardiac arrhythmias). Other tools include the AR xVision[55] three-dimensional anatomical images that enable clinical providers to see a patient's skin and tissue (akin to x-ray vision) and the AR SureWash[56] mobile app, which provides personalised feedback for hand hygiene technique[57]. VR technologies were also implemented during the COVID-19 pandemic when face-to-face teaching was not possible[58]. For example, St Bartholomew's Hospital used VR to train their nurses and doctors on 50 clinical procedures[59]. Their OMS VR system provided performance feedback, tracked improvement and facilitated group learning.

Gap in research and aim

Despite the emergence and potential efficacy of simulation technologies, the effectiveness of these technologies as an educational intervention remains debated. This includes how good they are at enabling upskilling compared to other strategies, and how they can be implemented into a practice setting, to enable upskilling. Additionally, as evident in the mixed findings on the effectiveness of AR and VR interventions in upskilling staff, programme interventions, including digital ones, do not work for everyone equally[60]. A gap in research remains on the factors that influence when an AR or VR intervention works, to what extent, for whom and in which context. Moreover, research is needed on the causal mechanisms that influence the outcomes of AR/VR interventions and their implementation. This is essential in ensuring that future digital interventions are designed and appropriately targeted at health and care workers, for both maximum efficiency and sustained effects. The aim of this review is to develop, test and refine an evidence-informed programme theory on what facilitates or constrains the implementation of AR or VR programmes in health and care settings and understand how, for whom and to what extent they 'work.'

42 METHODS AND ANALYSIS

44 Realist review

46 This research will take a realist approach because it can produce useful answers to complex questions47 often left unexplored by experimental research[60]. These questions include: how, when, for whom

and to what extent, does an intervention 'work'? To answer these questions, realist approaches consider the complex interactions between the environment, individuals and the intervention. Realist evaluation is an emerging theory-driven methodology that seeks to understand CMO configurations, i.e. the context (C), mechanisms (M) and outcomes (O) of interventions. Context refers to the backdrop of conditions that may impact outcomes, such as organisational structure, functional fidelity, environmental settings, culture and norms. These trigger or modify mechanisms (causal forces) that influence outcomes[61]. Examples of mechanisms include the resources offered by interventions or changes in reasoning or behaviour. Realist reviews seek to understand context, mechanisms and outcomes, by identifying candidate theories and then systematically reviewing literature for underlying social entities, processes or social structures that result in the intended outcome [62]; rather than assuming that the intervention itself produces an outcome. This process is useful for complex interventions, in which outcomes may not necessarily be linear, and instead depend on the context and both intended and unintentional mechanisms[62]. It also allows exploring how an intervention is meant to work compared to how it actually works in practice[63]. Additionally, 'demi-regularities' are identified to acknowledge that outcomes will vary across contexts, but some CMO patterns will remain[61]. This focuses reviewers on the transferable aspects of a programme theory [62]. By definition, candidate theories are individual and specific theories, while a programme theory provides an over-arching explanation of how a specific intervention is expected to 'work,' including how contexts and mechanisms lead to negative and positive outcomes[64]. CMO configurations are then developed as a programme theory, which is tested and refined in real-life settings and with key stakeholders[60]. As with AR/VR technologies, the main benefit of realist evaluation is the ability to bridge theory and practical application in the contexts and with the populations that the intervention targets[60]. A realist review will therefore help to answer the following questions: What facilitates or constrains the implementation of AR/VR programmes in health and care • settings? What are the mechanisms by which VR/AR interventions result in their intended outcomes? • What contexts determine whether the different mechanisms produce their intended outcomes? • • In what circumstances and for whom are VR/AR interventions effective in upskilling health and care providers? The core research team is a multi-disciplinary group of researchers, from the backgrounds of nursing, primary healthcare, health informatics and implementation. Across this group, expertise relevant to the topic includes that on digital health innovation and evaluation, behaviour change, implementation science and conducting realist reviews. The RAMESES training documents[62] will be referred to, and the review will be reported in accordance with the RAMESES Publication Standards for Realist Synthesis[65] (supplementary Table S1). **Procedures** Realist reviews tend to follow a three-step process: theory elicitation, theory testing, and theory refinement. This process will be followed to describe our procedures. Unlike systematic reviews,

1	which aim to uncover all research relevant to the t	opic realist reviews find a comprehensive balance
		• •
	* * * *	
	1. Theory elicitation	
	Search strategy	
	A search will be conducted to identify initial cand	idate theories. These will not be limited by
		•
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	We will identify academic and practitioner theorie	s using free text and MeSH terms when searching
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	which 200 were deemed potentiarly englote, after	reviewing their titles and abstracts.
	We will focus on the discussion section of items t	o identify why AR or VR interventions did or did
		include the author's theories[07]. Existing
	systematic reviews will first be reviewed.	
	Relevant practitioner theories may be presented by	professional hodies or within grey literature
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		gi the database searches, as they are indexed in
	Wiednite.	
	Table 1 Summary of relevant journals related to c	ontinued learning in health and care
	Table 1. Summary of relevant journals related to e	ontilided learning in learning and eare
52	Professional Body	Journal/s
	•	Academic Medicine; MedEdPORTAL
	rissention of rindrean model coneges	readenie inductie, nedelai orenne
	Association for Medical Education in Europe	Medical Teacher
	issolution for medical Education in Europe	
	Foundation for Advancement of International	International Journal of Medical Education
	Foundation for Advancement of International Medical Education and Research	International Journal of Medical Education
	Foundation for Advancement of International Medical Education and Research	International Journal of Medical Education
	Medical Education and Research	
	Medical Education and Research Alliance for Continuing Education in the Health	Journal of Continuing Education in the Health
	Medical Education and Research Alliance for Continuing Education in the Health Professions; Association for Hospital Medical	
	Medical Education and Research Alliance for Continuing Education in the Health Professions; Association for Hospital Medical Education; Society for Academic Continuing	Journal of Continuing Education in the Health
	Medical Education and Research Alliance for Continuing Education in the Health Professions; Association for Hospital Medical	Journal of Continuing Education in the Health
	Medical Education and Research Alliance for Continuing Education in the Health Professions; Association for Hospital Medical Education; Society for Academic Continuing Medical Education	Journal of Continuing Education in the Health Professions
	Medical Education and Research Alliance for Continuing Education in the Health Professions; Association for Hospital Medical Education; Society for Academic Continuing	Journal of Continuing Education in the Health
	$1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ 10 \\ 11 \\ 12 \\ 13 \\ 14 \\ 15 \\ 16 \\ 17 \\ 18 \\ 19 \\ 20 \\ 21 \\ 23 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 31 \\ 32 \\$	 of empirical research and theory[66]. Searches will searching may alter the following procedures. Figu- in each stage. <i>I. Theory elicitation</i> <u>Search strategy</u> A search will be conducted to identify initial cand publication date and are characterised as academic theories. We will identify academic and practitioner theorie Medline, SCOPUS, CINAHL, EMBASE, Educati We b of Science. Snowballing will also help to ide provides the search strategy. An initial search of th which 200 were deemed potentially eligible, after We will focus on the discussion section of items, t not achieve their intended outcomes. These often i systematic reviews will first be reviewed. Relevant practitioner theories may be presented by including editorials, letters, news articles and com above search with the additional journals presente Medline. Table 1. Summary of relevant journals related to c

The Australian & New Zealand Association for Health Professional Educators	or Focus on Health Professional Education
Association for the Study of Medical Education	on Medical Education
Journals not associated with a professional	body
Journal of Nursing Education and Practice	
Nurse Education Today	
International Journal of Nursing Studies	
We will also identify theories related to adult	learning from the academic articles. These are exp
to include theories related to adult learning for	r health and care professionals, including the Scho
	ick's[70] theory on how physicians learn. Two the
	ey to professional learning are directly applicable
AR/VR. These include:	
	edge construction and learning are facilitated through
	b[72] proposes a framework for experiential learn ective observation, abstract conceptualisation, and
active experimentation.	
*	ough interaction between previous skills/knowledg
	n and social activities, within the learner's environ
physical and social world[73]. Simula	tion has been identified as a tool that supports
•	ructivists generally believe that people learn best b
'doing,' as this is how they construct t	their knowledge[76].
Theories may also relate to technology accept	ance and adoption. Frameworks include:
	77], which explains how and at what rate innovatio
	ned by different categories of adopters. This can be
 applied to organisations and individua The Technology Acceptance Model[7 	us. 8] explains that an individual's perceived usefulne
and ease–of-use of a technology influe	
	d Use of Technology[79] determines that four
	effort expectancy; social influence; and, facilitatin
	ce and voluntariness of use) influence an individua
technology use and acceptance.	
	reasons for non-adoption, abandonment, and
	six domains (condition, technology, value propos
adopter system and institutional and s • The Consolidated Framework for Imp	ocietal contexts). lementation Research[81] considers five domains
	nner settings, the individuals involved and
implementation process.	0,

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3	1	• The Normalisation Process Theory[82] focuses on people's actions, rather than their
4	1 2 3	intentions/beliefs. It considers coherence, cognitive participation, collective action and
5	3	reflexive monitoring as crucial to the implementation process.
6 7	4	
8	5	Record management
9	6	
10	7	Similar to the methods in Randell et al.[63], records will be saved to an Endnote library, as well as
11	8	charted on Excel. A timeline sheet on Excel will record search activities, including the databases
12 13	9	searched, the date of each search and the number of records found.
14	10	
15	11	Screening
16	12	
17	13	Two researchers (NG and DD) will screen the literature for eligibility, starting by determining the
18	14	relevance from the title and abstract, and then reading the full-text. As in other realist reviews, the
19 20	15	first researcher will screen all items and generate a short-list of possible eligible items, while the
21	16	second independently screens a random sub-set of items (20%) at each screening stage[83]. A raw
22	17	agreement rate will be calculated to determine interrater reliability, while any disagreements will be
23	18 19	resolved through discussion, so that consensus is met. The inclusion criteria for the academic and practitioner theories will be:
24	20	 Using simulation technologies (any type of immersion will be accepted)
25 26	20 21	
20		• Health and care workers and individuals post-graduation/registration as learners.
28	22	• Any health, care or university-based setting (as these often have simulation labs)
29	23	• Includes detail on implementation and/or on what contexts, how and for whom they 'worked.'
30	24	Published in English
31 32	25	
33	26	The exclusion criteria include simulation technologies that do not use augmentation or VR (e.g. low
34	27	fidelity web-based e-learning interventions or manikin-only simulators), undergraduate students and
35	28	published in languages other than English. Work also including undergraduate learners or other
36	29	simulation technologies will only be included if the data for post-graduate/registered learners and
37 38	30	AR/VR can be separated. Undergraduate students will be excluded as they differ from learners post-
39	31	registration. Namely, they are learning content for the first time, rather than upskilling their clinical or
40	32	practical knowledge/experience. For the purpose of this review, VR is defined as a computer-
41	33	generated simulated environment, while AR refers to the projection of computer-generated imagery
42	34	onto real-world environments[84,85].
43 44	35	
44	36	A PRISMA flowchart[86] will document the review selection and decision process.
46	37	
47	38	Analysis and synthesis
48	39	
49 50	40	We will extract relevant information (presented in Box 1) including that pertaining to context,
51	41	mechanism and outcomes from each article from the academic and practitioner theories. Adult
52	42	learning and technology adoption theories will be briefly summarised. For consistency, outcomes
53	43	should broadly be related to the Kirkpatrick et al.[87] components of evaluation: reaction (i.e.
54	44	satisfaction), learning (i.e. knowledge), behaviour or results (skills). Unintended and other subjective
55 56	45	or observed outcomes (e.g. increased confidence or perceived interactivity) will be included too. A
56 57	46	second reviewer will code and extract data from a random selection of 10-20% of the articles to
58	47	ensure consistency in interpretation.
59	48	
60	49	

2	
	• Author; date
	• Title
	• Type of publication (journal paper, conference paper or book chapter)
	• Research design, theoretical orientation (if applicable) and methods
	AR/VR technology description
	• Study objective (focus)
	• Setting; country
	• Sample (type, size, age, gender)
	 Context
	Mechanism
	• Outcome (intended, unintended and/or subjective)
	• Implementation (strategy, adoption and/or uptake)
	• Learning or technology adoption theories mentioned (if applicable)
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4	
5	All information will be recorded in an Excel sheet for analysis. If possible, complete CMO
6	configurations will be recorded, however; it is unlikely that all articles will contain complete
7	statements- fragments will therefore be recorded too[63].
8	
9	Upon completion, we will conduct a narrative synthesis to determine any overlapping CMO
10	configurations. These will then be compared with identified (learning and adoption) theories to furth
11	explore the underlying causal mechanisms so as to understand how VR/AR interventions can or
12	should upskill health and care professionals[88]. The resulting CMO configurations will answer (a)
13	what facilitates or constrains the implementation of AR/VR programmes in health and care settings?
14	(b) How, for whom and to what extent did they produce the intended outcomes (reaction/satisfaction
14 15	(b) How, for whom and to what extent did they produce the intended outcomes (reaction/satisfaction short and long-term learning/knowledge and behaviour/results)?
15	short and long-term learning/knowledge and behaviour/results)?
15 16	short and long-term learning/knowledge and behaviour/results)?
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The articles will be screened by determining their relevance to the programme theory (e.g. AR/VR tools used by health and care workers). A benefit of realist reviews is the focus on the intervention mechanism, enabling the inclusion of literature whereby the intervention has been applied to different settings, people or even similar interventions in the same setting[68,89]. All study designs will be included. A PRISMA diagram will visualise the study selection process[86].

Analysis and synthesis

Relevant information (presented in Box 1) will be extracted into an excel sheet. We will also assess the quality of each paper using the Mixed Methods Appraisal Tool (MMAT), as this is appropriate for qualitative, quantitative and mixed methods research[90]. The MMAT was developed in 2007[91], and revised in 2011[92]. Unlike earlier versions, the newest 2018 MMAT is not intended to be quantified and instead offers a guide for discussing quality. We will therefore highlight methodological flaws to inform recommendations for future research. Low quality research will not be excluded, as realist methodologists acknowledge that useful information on contextual factors may be present[93]. In alignment with the guidelines for conducting realist reviews, the quality of each study will focus on the evidential fragment (relevant section) that each theory is drawn from [93]. For example, when only quantitative data is used from a mixed-methods study to test the theory, the quality of the qualitative component will not be assessed. Cohen's kappa will be calculated, to determine interrater reliability between the two authors conducting the quality assessments.

3. Theory refinement

Coded data will be compared to the initial programme theory, and differences will be identified to refine and revise the programme theory. Upon completion of the final theory, a narrative and diagrammatic summary will be presented[64,94]. We will use the MMAT to assess the extent to which we are confident in each finding. Ultimately, each CMO configuration will be rated as high, moderate, low or very low in confidence. This rating will highlight areas for research and also support decision-makers when deciding whether to implement or develop similar technologies to upskill health and care workers.

Strengths and limitations

Inherent limitations of realist reviews must be acknowledged. Realist reviews have been critiqued to be laborious and time-intensive[95], so the included literature is not always up-to-date when it is published. We will overcome this through a second database search, which will specifically identify recently published work. Programme theories are also only as good as the literature they include, but they do sometimes not acknowledge or assess quality[83]. We are therefore conducting quality assessments of the literature and using this to identify our confidence in each CMO configuration. A fundamental limitation we cannot overcome but must acknowledge is that mechanisms are often untested and subjective author hypotheses[96], which may limit the accuracy of the programme theory.

44 Patient and public involvement

46 Members of the public were not involved in the development of this protocol.

60 48 ETHICS, DISSEMINATION AND CONCLUSION

1	
2	Ethics approval is not required to conduct this realist review. This protocol describes how we will
3	
	conduct a realist review that constructs, tests and refines an evidence-informed programme theory on
4	what facilitates or constrains the implementation of AR/VR programmes in health and care settings
5	and how, for whom and to what extent they 'work.' The results may inform and support AR/VR
6	interventions from clinical educators, healthcare providers and software developers. Upskilling
7	through AR/VR learning interventions may ultimately improve quality of care and promote evidence-
8	based practice and continued learning. Findings will be disseminated through conference
9	presentations and peer-reviewed journal publications. In our future work we will continue to refine
10	our programme theory, by involving stakeholders. This will include interviews, as well as
11	experimental work.
12	experimental work.
12	AUTHOR CONTRIBUTIONS
	AUTHOR CONTRIBUTIONS
14	
15	NG conceived and designed the study with support from DD, SNVDV and PW. NG wrote the first
16	draft of the manuscript. All authors revised and approved the final manuscript.
17	
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19	
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21	Greater Manchester. The views expressed in this publication are those of the authors and not
22	necessarily those of the National Institute for Health Research or the Department of Health and Social
23	Care. Grant number: N/A.
23	
24	
	COMPETING INTERESTS
26	
27	The authors have no competing interests to declare.
28	
29	PATIENT CONSENT FOR PUBLICATION
30	
31	Not required.
32	
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52	47	Targeting Substance Use: Realist Review. J Med Internet Res 2021;23(1):e20557
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58	52	FIGURE LEGENDS
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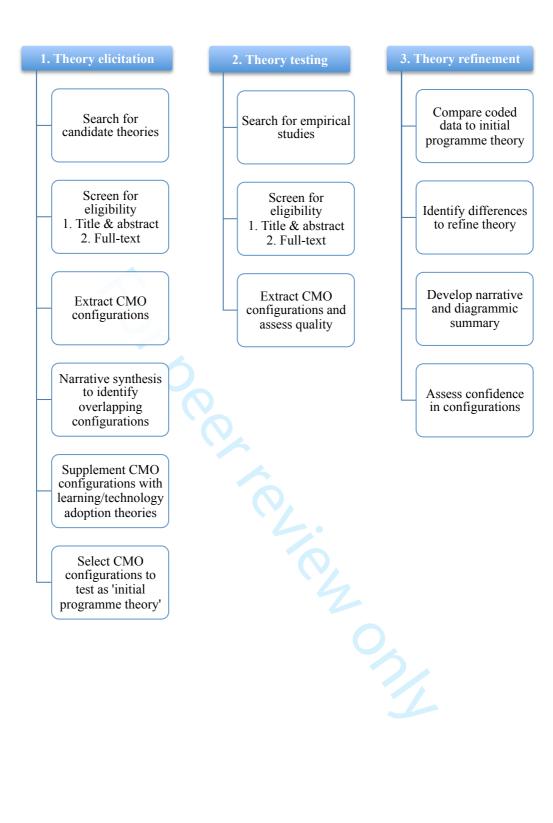
1 Figure 1. Summary of the three steps and process that will be conducted. CMO stands for Context

to beet terien only

2 Mechanism and Outcome.

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Supplementary file

Table S1. Completed checklist of the RAMESES Publication Standards for realist reviews¹

No.	Section /	Checklist item	Rep	orted
	Торіс		Yes	N/A
Title				
1.		In the title, identify the document as a realist synthesis or	Х	
		review.		
Absti	ract			
2.		While acknowledging publication requirements and	Х	
		house style, abstracts should ideally contain brief details		
		of: the study's background, review question or		
		objectives; search strategy; methods of selection,		
		appraisal, analysis and synthesis of sources; main		
		results; and implications for practice		
Intro	duction			
3.	Rationale for	Explain why the review is needed and what it is likely to	Х	
	review	contribute to existing understanding of the topic area.		
4.	Objectives	State the objective(s) of the review and/or the review	Х	
	and focus of	question(s). Define and provide a rationale for the focus		
	review	of the review.		
Meth	ods			1
5.	Changes in	Any changes made to the review process that was		X
	the review	initially planned should be briefly described and		
	process	justified.		
6.	Rationale for	Explain why realist synthesis was considered the most	Х	
	using realist	appropriate method to use.		
	synthesis			
7.	Scoping the	Describe and justify the initial process of exploratory	Х	
	literature	scoping of the literature.		
8.	Searching	While considering specific requirements of the journal	Х	
	processes	or other publication outlet, state and provide a rationale		
	^	for how the iterative searching was done. Provide details		
		on all the sources accessed for information in the review.		
		Where searching in electronic databases has taken place,		
		the details should include, for example, name of		
		database, search terms, dates of coverage and date last		
		searched. If individuals familiar with the relevant		
		literature and/or topic area were contacted, indicate how		
		they were identified and selected.		
9.	Selection and	Explain how judgements were made about including and	Х	
	appraisal of	excluding data from documents, and justify these.		
	documents			
10.	Data	Describe and explain which data or information were	Х	1
	extraction	extracted from the included documents and justify this		

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Analysis and	selection.		
Analysis and			
-	Describe the analysis and synthesis processes in detail.	Х	
synthesis	This section should include information on the		
processes	constructs analysed and describe the analytic process.		
lts			
Document	Provide details on the number of documents assessed for		X
flow diagram	eligibility and included in the review with reasons for		
	exclusion at each stage as well as an indication of their		
	source of origin (for example, from searching databases,		
	reference lists and so on). You may consider using the		
	example templates (which are likely to need		
	modification to suit the data) that are provided.		
Document	Provide information on the characteristics of the		Х
characteristic	documents included in the review.		
S			
Main	Present the key findings with a specific focus on theory		Х
findings	building and testing.		
ssion			
Summary of	Summarise the main findings, taking into account the		X
findings	review's objective(s), research question(s), focus and		
	intended audience(s).		
Strengths,	Discuss both the strengths of the review and its		Х
limitations	limitations. These should include (but need not be		
and future	restricted to) (a) consideration of all the steps in the		
research	review process and (b) comment on the overall strength		
directions	of evidence supporting the explanatory insights which		
	emerged.		
	The limitations identified may point to areas where		
	further work is needed.		
Comparison	Where applicable, compare and contrast the review's		Х
with existing	findings with the existing literature (for example, other		
literature	reviews) on the same topic.		
Conclusion	List the main implications of the findings and place		X
and	these in the context of other relevant literature. If		
recommendat	appropriate, offer recommendations for policy and		
ions			
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	ts Document flow diagram Document flow diagram Document characteristic s Main findings ssion Summary of findings Strengths, limitations and future research directions Comparison with existing literature Conclusion and recommendat	ts Document flow diagram Provide details on the number of documents assessed for eligibility and included in the review with reasons for exclusion at each stage as well as an indication of their source of origin (for example, from searching databases, reference lists and so on). You may consider using the example templates (which are likely to need modification to suit the data) that are provided. Document characteristic Provide information on the characteristics of the documents included in the review. s Main findings Present the key findings with a specific focus on theory building and testing. ssion Summarise the main findings, taking into account the review's objective(s), research question(s), focus and intended audience(s). Strengths, limitations and future research directions Discuss both the strengths of the review and its limitations. These should include (but need not be restricted to) (a) consideration of all the steps in the restricted to) (a) consideration of all the steps in the research directions Of evidence supporting the explanatory insights which emerged. The limitations identified may point to areas where further work is needed. Comparison with existing literature Where applicable, compare and contrast the review's findings with the existing literature (for example, other reviews) on the same topic. Conclusion and ions List the main implications of the findings and place these in the context of other relevant literature. If appropriate, offer recommendations for policy and practice.	ts Provide details on the number of documents assessed for eligibility and included in the review with reasons for exclusion at each stage as well as an indication of their source of origin (for example, from searching databases, reference lists and so on). You may consider using the example templates (which are likely to need modification to suit the data) that are provided. Document characteristic Provide information on the characteristics of the documents included in the review. S Provide information on the characteristics of the documents included in the review. S Summary of findings Summary of findings Summarise the main findings, taking into account the review's objective(s), research question(s), focus and intended audience(s). Strengths, limitations Discuss both the strengths of the review and its limitations. These should include (but need not be restricted to) (a) consideration of all the steps in the review process and (b) comment on the overall strength of evidence supporting the explanatory insights which emerged. Comparison with existing literature List the main implications of the findings and place these in the context of other relevant literature. If appropriate, offer recommendations for policy and practice. Funding Provide details of funding source (if any) for the review, the role played by the funder (if any) and any conflicts

¹Wong, G., Greenhalgh, T., Westhorp, G., et al. RAMESES publication standards: realist syntheses. *BMC Medicine* 2013;11(1):21.

Databases	Medline
	SCOPUS
	CINAHL
	EMBASE
	Education Resource Information Centre
	PsycINFO
	Web of Science
Keywords	
Technology/Intervention	augmented reality
	• virtual reality
Population/sample	• health*
	healthcare; health; health worker; heal
	staff; health provider
	• care*
	care; carer; caregiving; caregiver; cari
	• nurs*
	nurse, nursing, nurses
	doctor
	• surgeon
Focus	• training
	• upskilling
	• skill
	• education
	• evaluation
	• implementation
	• feasibility
	effectiveness
Example with Boolean operators	
	(TITLE-ABS-KEY (augmented AND reality
	OR virtual AND reality) AND TITLE-ABS
	KEY (health* OR care* OR nurs* OR doo
	OR surgeon) AND TITLE-ABS-KEY (
	training OR upskilling OR skill OR educat
) AND TITLE-ABS-KEY (evaluation OR
	implementation OR feasibility OR
	effectiveness))

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No.	Section / Topic	Checklist item	Reported	
			Yes	N/A
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		they were identified and selected.		
9.	Selection and	Explain how judgements were made about including and	Х	
	appraisal of	excluding data from documents, and justify these.		
	documents			
10.	Data	Describe and explain which data or information were	Х	
	extraction	extracted from the included documents and justify this		
		selection.		

11.	Analysis and synthesis processes	Describe the analysis and synthesis processes in detail. This section should include information on the constructs analysed and describe the analytic process.	Х	
Resu	lts			
12.	Document flow diagram	Provide details on the number of documents assessed for eligibility and included in the review with reasons for exclusion at each stage as well as an indication of their source of origin (for example, from searching databases, reference lists and so on). You may consider using the example templates (which are likely to need modification to suit the data) that are provided.		X
13.	Document characteristic s	Provide information on the characteristics of the documents included in the review.		X
14.	Main findings	Present the key findings with a specific focus on theory building and testing.		X
Discu	ission			
15.	Summary of findings	Summarise the main findings, taking into account the review's objective(s), research question(s), focus and intended audience(s).		X
16.	Strengths, limitations and future research directions	Discuss both the strengths of the review and its limitations. These should include (but need not be restricted to) (a) consideration of all the steps in the review process and (b) comment on the overall strength of evidence supporting the explanatory insights which emerged. The limitations identified may point to areas where further work is needed.		X
17.	Comparison with existing literature	Where applicable, compare and contrast the review's findings with the existing literature (for example, other reviews) on the same topic.		X
18.	Conclusion and recommendat ions	List the main implications of the findings and place these in the context of other relevant literature. If appropriate, offer recommendations for policy and practice.		X
19.	Funding	Provide details of funding source (if any) for the review, the role played by the funder (if any) and any conflicts of interests of the reviewers.	Х	

¹Wong, G., Greenhalgh, T., Westhorp, G., et al. RAMESES publication standards: realist syntheses. *BMC Medicine* 2013;11(1):21.