FULL/LONG TITLE OF THE STUDY

Impact of systematic user testing of written guidance on the rate of moderate to severe errors made by hospital nurses during *in situ* simulation of the preparation and administration of an intravenous medicine: phase 2 – *in situ* simulation

SHORT STUDY TITLE / ACRONYM

Effects of user testing injectable medicines guidance – phase 2

PROTOCOL VERSION NUMBER AND DATE

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RESEARCH REFERENCE NUMBERS

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The structure of this protocol is based on the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist, with adaptions suitable for an *in situ* simulation study.

LIST of CONTENTS

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STUDY SUMMARY

Study Title	Impact of systematic user testing of written guidance on the rate of moderate to severe errors made by hospital nurses during *in situ* simulation of the preparation and administration of an intravenous medicine: phase 2 – *in situ* simulation
Short title	Effects of user testing injectable medicines guidance – phase 2
Study Design	Single-blind, randomised parallel group *in situ* simulation experiment
Study Participants	Qualified nurses or midwives registered with the Nursing and Midwifery Council, who are authorised to prepare and administer intravenous medicines in a hospital and who have done this during at least 50% of working shifts during the past six months (or since authorisation to prepare and administer intravenous medicines if this was granted more recently).
Planned Size of Sample (if applicable)	121-172 participants per group
Follow up duration (if applicable)	N/A
Planned Study Period	October 2018 to July 2019
Research Question/Aim(s)	Research question (whole study): Is it possible to reduce the incidence of medication errors by improving the content, wording, structure and formatting of written documents providing technical information to health professionals? Objectives for the entire study are: 1. To identify and resolve problems in a typical NHS Injectable Medicines Guide (IMG) monograph using systematic user testing. 2. To compare the rates of preparation and administration errors associated with use of the original and user testing developed IMG monograph. 3. To determine whether systematic user testing of the IMG is a cost-effective approach to improving patient safety. 4. To advise the IMG Advisory Board on generic lessons learned during user testing that could be introduced to the entire guide during the next revision cycle. Only objective 2 will be addressed during phase 2 of the study (this protocol).

FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
National Institute for Health Research, Trainees Co-ordinating Centre, Leeds Innovation Centre, 103 Clarendon Road, Leeds, LS2 9DF. Telephone: 0113 346 6260 Fax: 0113 346 6272 Email: tcc@nihr.ac.uk	£173,064
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ROLE OF STUDY SPONSOR AND FUNDER

The funder had/will have no influence on the design, conduct, data analysis and interpretation, manuscript writing and dissemination of results associated with this study. The sponsor had/will have final approval on the design and conduct of this study, but no influence on the data analysis and interpretation, manuscript writing and dissemination of results associated with this study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Study Advisory Group

A Study Advisory Group has been established to:

- Provide advice and support
- Provide advice on current NHS priorities in this area
- Provide advice on current NHS practice in this area
- Oversee the completion of the project in accordance with the principles of Good Clinical Practice
- Advise and assist with dissemination of findings to NHS stakeholders

The group is made up of practising nurses, pharmacists and doctors with expertise in medicines safety and the administration of injectable medicines. This group can be considered independent of the investigators and sponsor, as it will chaired by a member who is not a researcher or employed by the sponsoring or funding organisations.

As the participants in this study will be NHS nurses, members of the Study Advisory Group will also play a participant involvement role, by providing advice on study design, study documentation and recruitment. Additional advice on study document design and recruitment will also be sought from independent nurses.

Lay Advisors

Two lay advisors will be recruited to assist with the dissemination of the findings of this study to a lay audience. They will be invited to observe user testing and the *in situ* simulation phases of this study and to share their experiences via suitable lay forums. They will also assist with the dissemination of the final results of the study to a lay audience.

Individuals

Dr Matthew Jones, NIHR Transitional Research Fellow, University of Bath will act as Chief Investigator. He will lead and carry out all aspects of the design, conduct, data analysis and interpretation, manuscript writing and dissemination of results associated with this study.

Prof Margaret Watson, University of Bath will provide research support to the Chief Investigator by providing expert advice and mentoring in relation to all aspects of the design, conduct, data analysis and interpretation, manuscript writing and dissemination of results associated with this study.

Prof DK Theo Raynor, University of Leeds, will provide training supervision to the Chief Investigator by providing expert advice and mentoring in relation to the design, conduct, data analysis and interpretation, manuscript writing and dissemination of results of the user testing work programme of this study.

Prof Bryony Dean Franklin, University College London, will provide training supervision to the Chief Investigator by providing expert advice and mentoring in relation to the design, conduct, data analysis and interpretation, manuscript writing and dissemination of results of the *in situ* simulation work programme of this study.

Dr Rebecca Kandiyali, University of Bristol, will provide training supervision to the Chief Investigator by providing expert advice and mentoring in relation to the design, conduct, data analysis and interpretation, manuscript writing and dissemination of results of the health economic analysis work programme of this study.

Dr Anita McGrogan, University of Bath, will provide advice on the statistical design and analysis of the *in situ* simulation study.

PROTOCOL CONTRIBUTORS

This protocol was written by the Chief Investigator (Dr Matthew Jones) with advice from Prof Bryony Dean Franklin (UCL) and Prof Margaret Watson (University of Bath), research advisors for this study. Advice on the statistical design and analysis was provided by Dr Anita McGrogan (University of Bath).

Potential research participants have been involved with the design of this study via the Study Advisory Group.

KEY WORDS: Injections, Intravenous
Medication Errors
Guideline Adherence
Information Science

STUDY PROTOCOL

1 INTRODUCTION

1.1 Background

There is little previous research investigating tools for preparing and testing technical information about medicines aimed at health professionals: only one study has been identified, which applied systematic user testing to improve the presentation of the Summary of Product Characteristics for two medicines[1].

A considerable number of studies have been carried out in the related fields of patient medicines information and clinical guideline production. In these areas, systematic user testing has been shown to improve understanding and decrease reading time[1-4]. Recently published guidance on the implementation of clinical guidelines recommends user testing[5] and it is required in the development of patient information leaflets for licensed medicines[4]. User testing is therefore considered the current "gold standard" method for improving patient information and the presentation of information to clinical guideline committees.

The major advantage of user testing is that it is based on potential users reading the document to locate key information and correctly use it to recommend appropriate actions and the reasons for them[4]. Problems and potential solutions are therefore identified. Iterative rounds of interviews with potential users are followed by document revision, until all problems are resolved[1,4,6]. Each interview involves direct questions to determine whether the interviewee can locate and use key points of information, followed by a semi-structured interview to explore opinions of more general issues (e.g. structure of the document, language used). This ensures that participants only give feedback once they have experience of using a document to locate information.

During phase 1 (described in a previous protocol), this study investigated the application of user testing to the NHS Injectable Medicines Guide (IMG). Standard user testing methodology was applied to revise the adult IMG monograph for a high-risk medicine. The "users" during this process were hospital and community nurses who regularly prepared and administered intravenous medicines.

In phase 2 (described by this protocol), the outcomes achieved as a result of user testing will be investigated, by measuring the effect of this process on the occurrence of injectable medicine preparation and administration errors in a randomised *in situ* simulation experiment carried out with hospital nurses on duty in their usual clinical environment.

1.2 Rationale

Medication errors are a serious and persistent problem in all healthcare systems. The number of reported errors has increased year-on-year, to more than 100,000 in England and Wales[7]. A review of reports between 2005 and 2010 found that 17% of errors resulted in patient harm, including 822 cases of death or severe harm[7]. The incidence of errors is higher for injectable medicines, with systematic reviews suggesting an error rate of 35-50%[8,9]. In November 2016, an alert was issued

highlighting 2200 reports since 2013 of incidents with just one intravenous medicine (phenytoin), resulting in four deaths, five cases of severe harm and 121 cases of moderate harm[10].

In 2007, the National Patient Safety Agency required healthcare providers to provide protocols for the administration of injectable medicines[11], such as the NHS Injectable Medicines Guide (IMG). This is used by nurses in more than 125 hospitals to guide the administration of individual doses and is accessed more than 1.5 million times per year[12,13]. Such guidance must be written carefully, as difficulty finding relevant, unambiguous information in technical documents has been linked to serious medication errors[14-16]. Systematic reviews of factors contributing to patient safety incidents therefore include contradictory, incomprehensible or poor quality information[17,18]. It is therefore concerning that the IMG has been described as too detailed and confusing to likely users[13,19]. This suggests that improvements to the presentation of the information in the IMG might result in fewer errors. Such concerns are shared by the IMG advisory board (Susan Keeling, IMG Project Manager, personal communication, 28/10/2016).

The IMG is therefore the ideal case study to use to investigate the wider question of whether improved written documents providing technical information to health professionals can reduce the incidence of medication errors.

As has already been discussed, systematic user testing is the gold standard approach for improving the quality of written documents. However, the effect of user testing medicines information on the behaviour of readers has not been previously investigated, as the previous studies outlined above have measured outcomes such as understanding and reading time[1-4]. This study will therefore add to the understanding of the outcomes achieved by user testing, by measuring the effect of this process on the occurrence of injectable preparation and administration errors.

We will compare error rates occurring during use of the user tested monograph and the original IMG monograph. This is an appropriate comparator as it was this version of the IMG which was used as the starting point of the user testing process. In addition, this version of the IMG represents current standard practice in many NHS hospitals. This comparator will therefore enable the research to determine whether the user testing process results in fewer injectable preparation and administration errors, and whether the user tested monograph results in fewer errors than the current standard IMG guide.

1.3 Research Question

Research question (whole study): Is it possible to reduce the incidence of medication errors by improving the content, wording, structure and formatting of written documents providing technical information to health professionals?

This question will be investigated using the NHS IMG as a case study relating to one of the highest risk routes of medicines administration.

1.4 Objectives

Objectives for the entire study are:

1. To identify and resolve problems in a typical NHS Injectable Medicines Guide (IMG) monograph using systematic user testing.
2. To compare the rates of preparation and administration errors associated with use of the original and user testing developed IMG monograph.
3. To determine whether systematic user testing of the IMG is a cost-effective approach to improving patient safety.
4. To advise the IMG Advisory Board on generic lessons learned during user testing which could be introduced to the entire guide during the next revision cycle.

Only objective 2 will be addressed during phase 2 of the study (this protocol).

1.5 Study design

This study will be a single-blind, randomised parallel group *in situ* simulation experiment with a 1:1 allocation ratio. It is designed to determine whether the user tested guide is superior to the original guide.

In situ simulation involves a simulated episode of patient care integrated into a clinical environment with participants who are on duty health professionals. It is therefore useful in patient safety research if it is not feasible to test interventions during routine patient care, while still allowing participants to experience the time pressures and distractions present in the clinical environment.[20]

During the simulation, each participant will prepare an infusion of an intravenous medicine ("bathicillin") in response to a simulated inpatient medication order for an adult. They will then administer this dose to a training manikin arm. During this process, they will be observed by a researcher, who will note any preparation or administration errors.

One group will use the "original" IMG monograph to guide this process and the other group will use the "user tested" IMG monograph. The groups will be treated identically in all other respects. As cross-over design will not be utilised, as this would create a serious order effect.

2 METHODS: PARTICIPANTS, INTERVENTIONS, DEFINITIONS AND OUTCOMES

2.1 Study setting

This study will be multi-centre and will take place in at least three hospitals, to increase the generalisability of the results. Any hospital in England that employs nurses who meet the participant inclusion and exclusion criteria (Section 2.2) will be eligible to be a study site. All sites will carry out the same activities, namely recruiting participants and hosting the *in situ* simulation.

2.2 Eligibility criteria

2.2.1 Inclusion criteria

- Qualified nurse or midwife registered with the Nursing and Midwifery Council
- Authorised to prepare and administer intravenous medicines in a hospital
- Has prepared and administered intravenous medicines during at least 50% of working shifts during the past six months (or since authorisation to prepare and administer intravenous medicines if this was granted more recently)
- At the time of data collection, actively working as a nurse in clinical area at usual hospital

2.2.2 Exclusion criteria

- Participated in phase 1 (user testing) of this study

2.3 Interventions

Participants will be allocated either the monograph revised via a user testing methodology (the "user tested monograph") or the "original monograph". Both monographs will give guidance on the intravenous administration of the same high-risk medicine (voriconazole). However, to prevent participants using prior knowledge of this medicine, both monographs will be "anonymised" by changing any mention of the medicine's generic name to "bathicillin". In addition, brand names will be changed to invented names. References to the use of an infusion pump will be removed, as such equipment may not always be readily available in study areas.

With the exception of the anonymisation described above, the "original monograph" will be identical to the IMG monograph in use at the start of phase 1 (user testing) of this study.

The "user tested monograph" will be the final result of the user testing carried out in phase 1 of this study. This process started with the "original monograph", which was then revised through three iterative cycles of identifying and resolving problems with the document by obtaining feedback from nurses as they used the document to locate and apply key information. Both monographs will therefore include the same content, but it will be presented differently.

In a survey of NHS organisations that use the IMG in clinical areas (carried out as part of the development of this protocol), 72 of 91 of responding organisations (79%) used the IMG mainly or entirely on computer screen. Therefore, the allocated monograph will be provided to the participants on a laptop computer screen at the start of the *in situ* simulation.

There will be no criteria for discontinuing or modifying the allocated monograph for any participant.

2.4 Definitions

An error will be considered to be any deviation in the preparation or administration of bathicillin from the simulated medication order, the hospital's intravenous drug administration policy and guidelines, or the IMG monograph[8,21,22]. Participants will not be required to assess the clinical appropriateness or

legal validity of the medication order. As this is a simulation study, deviations from procedures designed to reduce the likelihood of a subsequent error will not be considered. In line with other recent studies, examples of such procedural deviations include tubing not being tagged and labelled in accordance with local policy and failure to document administration of bathicillin in line with hospital policy[22]. In addition, errors relating to the safe handling of sharps will not be considered.

An "IMG-related error" will be an error in a process that requires use of information from the IMG. This does not mean that the error was definitely caused by the IMG, but the IMG had the potential to influence it. All other errors will be classified as "non-IMG-related errors".

Table 1 shows the definitions of error types that will be used in this study and whether they are classified as "IMG-related errors" or "non-IMG-related errors". These error types were developed by combining the typologies employed in previous research[8,14,22-27] and the requirements of national guidelines[28,29]. Certain types of error (e.g. omitted dose, wrong patient) are not included in Table 1, as they are not relevant to this study, due to the investigation of a single dose of one simulated medicine administered at a single time point.

Table 1: definitions of error types and categorisation as "IMG-related errors" or "non-IMG-related errors"

Error type	Definition	Error code
IMG related errors – an error in a process that requires use of information from the IMG		
Wrong reconstituting fluid	The dose is reconstituted with a different fluid to that specified in the IMG monograph	I1
Wrong reconstituting fluid volume	The dose is reconstituted with a volume of fluid which differs from that specified in the IMG monograph by ≥10%	I2
Dose discrepancy	The administered dose differs from the prescribed dose by ≥5%[a]	I3
Wrong diluent	The dose is infused in a different diluent to that specified in the IMG monograph	I4
Wrong diluent volume	The dose is infused in a different volume of diluent to that specified in the IMG monograph	I5
Incorrect technique (IMG related)	The dose is prepared or administered in a way that does not meet the requirements specified by the IMG monograph, e.g. the vial is shaken when the monograph specifies "do not shake".	I6
Wrong route	The dose is administered via a different route to that specified on the medication order	I7
Flush error	The intravenous cannula is not flushed in accordance with hospital policy before administration of the dose. (Any requirements for a flush after administration are not relevant, as the infusion will not be observed for its entire duration).	I8
Rate discrepancy	The dose is administered at a rate that differs from that specified in the IMG monograph by ≥10%	I9
Infusion expiry error	An infusion is labelled with an expiry date and time that is not in accordance with the IMG monograph	I10

Other IMG related error	Any IMG related error which does not fit one of the above categories	I11

Non-IMG-related errors – an error in a process that did not require use of information from the IMG		
Wrong medication	A different medication to that specified on the medication order is administered	N1
Incorrect technique (non-IMG related)	The dose is prepared or administered in a way that does not meet the requirements of hospital policy, e.g. incorrect mixing technique, air in the syringe, where these details are not specified in the IMG monograph.	N2
Non-aseptic technique	Breach of the aseptic technique policy of the hospital during the preparation or administration of the dose (e.g. hands not washed, vials/additive ports not swapped with an alcohol wipe)	N3
Expired ingredients	Use of expired medicine, reconstituting fluid, diluent or flush.	N4
Other non-IMG related error	Any non-IMG related error which does not fit the above categories	N5

[a]*A figure of 5% has been deliberately chosen, to ensure that an error is recorded when the participant does not account for the displacement value. This was a common error during the user testing phase. A threshold of 5% has been used in a number of previous studies[30].*

The potential clinical significance of all observed errors will be scored and then classified as minor, moderate or severe, using the expert panel method described in sections 4.1 and 4.3

2.5 Outcomes

2.5.1 Primary outcome

The primary outcome will be the observed rate of IMG-related moderate-severe errors in each group. Following the approach of recent meta-analyses, error rates will be expressed as percentages using the number of doses considered to have one or more errors as the numerator and the total number of doses as the denominator[8,16].

2.5.2 Secondary outcomes

There will be a number of secondary outcomes:

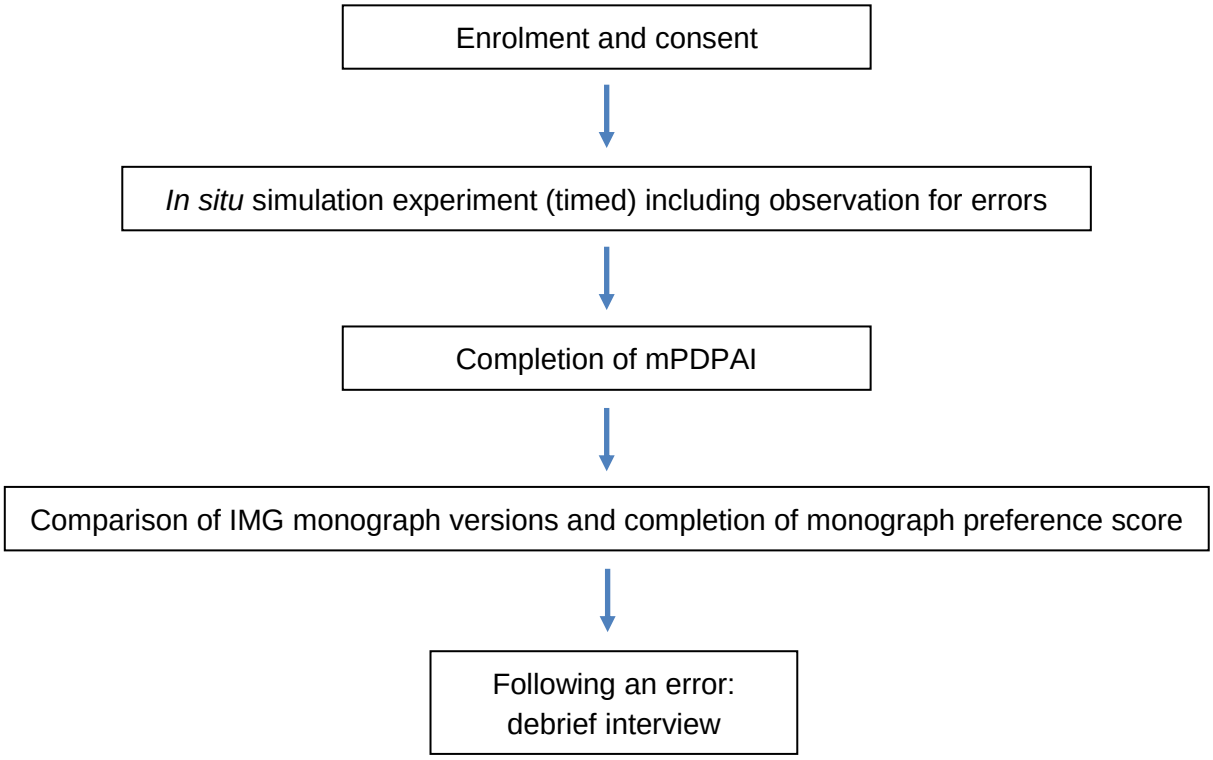
- The rate of IMG-related errors of any severity in each group
- The rate of moderate-severe non-IMG-related errors. This outcome will be measured because it is hypothesised that a more easily understood IMG monograph will enable participants to concentrate more on other aspects of the injection preparation and administration process.
- The rate of non-IMG-related errors of any severity in each group
- The mean time taken to prepare and administer the dose for each group. For each participant, the time will be measured from the point at which they start to read the simulated medication order or IMG monograph until the point at which they inform the observer that they would leave the simulated patient's bedside with the infusion running. This outcome will be measured

because it is hypothesised that a more easily understood IMG monograph will be read and interpreted more quickly, thus reducing the time required to prepare and administer the dose.

- The mean modified Decision Conflict Score (mDCS) for each group[31]. This will be calculated from participant's responses to a modified Provider Decision Process Assessment Instrument (mPDPAI) immediately after they have finished preparing and administering the intravenous infusion. The mDCS is a measure of participants' degree of knowledge and uncertainty whilst making decisions during the preparation and administration of the medicine. It will be measured because it is hypothesised that a more easily understood IMG will result in participants having great confidence in the decisions made during the dose preparation and administration process.
- The mean monograph preference score of each group. Immediately after completing the mPDPAI, each participant will be shown the version of the IMG monograph they did not use to prepare the dose of medicine and asked to rate their preferred version using a seven point Likert scale. This will be measured because it is hypothesised that participants will prefer the more easily used IMG.

2.6 Participant timeline

All study procedures will take place sequentially on the same day:



2.7 Sample size

There is one published study that reports the rate of moderate to severe errors in the preparation and administration of intravenous medicines to adults on UK hospital wards and which used the same error observation and severity determination techniques as this study[23]. This study observed one or more moderate-severe errors in 30% of 430 intravenous doses. If the definitions to be used for the current study had been applied in this previous research, 27.2% of 430 intravenous doses would have involved one or more moderate-severe IMG-related errors[23].

Using the same techniques, a larger and more recent, but as yet unpublished study, observed one or more moderate-severe preparation errors in 28% of 1148 adult injectable medicine doses administered on UK hospital wards[32]. This study did not investigate administration errors, but their inclusion would have increased this error rate.

These error rates are supported by other studies, which either took place in other countries or used different severity determination methods, which report similar rates of moderate-severe preparation and administration errors (22-34% of doses)[24,25,33].

Therefore, it is reasonable to assume that participants in the “original monograph” group will make at least one moderate-severe IMG-related error in 30% of doses.

Following discussion with the Study Advisory Group, it was agreed that at least one moderate-severe error occurring in 15% of doses would represent a clinically relevant reduction. This is in line with the assumptions underlying other recent research considering the effect of educational interventions on the rate of injectable medicine preparation and administration errors[34].

Standard calculations indicate that a sample size of 121 participants per group will give an 80% probability of detecting this reduction in the moderate-severe error rate at the 5% significance level, assuming equal group size[35]. This assumes that there is no clustering of the data by hospital site, as NHS hospitals are required to provide similar training for staff preparing and administering intravenous medicines, and to follow similar procedures[11,29].

A power calculation accounting for clustering (using STATA) indicates that a sample size of 43 participants per group per cluster will give an 80% probability of detecting the above reduction in the moderate-severe error rate at the 5% significance level. This assumes an intraclass correlation coefficient of 0.01, which is low, but justifiable given the similarities in nurse training and procedures discussed above. As it is anticipated that four hospitals is the most likely number of study sites, this equates to a sample size of 172 participants per group.

Given that likely recruitment rates are not accurately known, this study will therefore achieve a minimum sample size of 121 participants per group, but may increase this up to 172 participants per group if recruitment is sufficiently quick. This larger sample size would provide greater power to analyse the effect of hospital site (and other variables, see Section 4.3) on the outcomes.

2.8 Recruitment

The Chief Investigator will agree suitable times to visit participating wards with the relevant ward managers and/or matrons. Ward managers will circulate study information to their nurses in advance of this time. At agreed times, the Chief Investigator will visit wards and confirm with the nurse in charge that staffing levels and patient care requirements mean it is still safe for data collection to proceed. He will then invite staff to participate in a data collection session and agree a safe time (that day) for this to happen.

3 METHODS: ASSIGNMENT OF INTERVENTIONS

3.1 Sequence generation

The allocation sequence will be generated using an online blocked randomisation list generator (www.sealedenvelope.com/simple-randomiser/v1/lists). A block size of 10 will be employed. Allocation will be stratified by research site and nursing experience, to ensure equal representation of nurses employed by different hospitals and with different levels of experience in each group.

Nursing experience will be measured by the total number of years each participant has been accredited for the administration of intravenous medicines, with two strata: <5 years and ≥5 years. A cut off of five years of experience preparing and administering intravenous medicines was chosen because evidence suggests that the number of errors with which a nurse is involved decreases over the first four to six years of their nursing experience[25,36-38]. In particular, one study found that the risk of intravenous medicine administration errors decreased with each year of a nurse's experience up to six years[25].

The allocation sequence will link each participant's unique randomisation code to their allocation groups: A or B.

3.2 Allocation concealment

Allocation will be concealed by use of an online randomisation service (www.sealedenvelope.com).

3.3 Implementation

The allocation sequence will be generated and uploaded to the online randomisation service by a person independent from the research team. The Chief Investigator will enrol participants and randomly assign them to one of the study groups.

3.4 Blinding

The Chief Investigator (responsible for allocation, data collection and analysis) will be blinded to the assignment of interventions. The online randomisation service will produce a unique randomisation code for each participant. The independent person who generates the allocation sequence will create a folder on the data collection laptop computer containing a copy of the appropriate monograph for each

randomisation code. The filenames of these monographs will be the randomisation code to which they are linked.

Once the online randomisation service has allocated a participant to a group, a privacy filter will be placed over the screen of the data collection laptop, which only permits a person looking directly at the screen to see it. This will prevent the observer (Chief Investigator) from learning which monograph is in use, and so he will be blinded during data collection. The participant will be asked to open the monograph file named with their randomisation code on the data collection laptop and to use this during the simulation. Before the file is opened, the Chief Investigator will double check the correct file has been selected.

Once data collection is complete, the independent person will reveal which randomisation codes were allocated to groups A and B, but not which monograph is associated with each group. Data will then be analysed for group A versus group B, and the type of monograph associated with each group will only be revealed once this is complete. In this way, the Chief Investigator will remain blinded during data analysis.

Participants will be required to read their allocated IMG monograph, so cannot be blinded to the intervention. However, they will be unaware of the content of the alternative IMG monograph until the last stage of data collection (completion of the preference score). They will also be asked to avoid revealing any information about their allocated IMG monograph to the investigator.

4 METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

4.1 Data collection methods

Observational data

All data will be collected from each participant during a single individual session. Each session will be arranged to take place whilst the participant is actively working as a nurse in a clinical area at their usual hospital. Each data collection session will take place in the room in the relevant clinical area that is normally used for the preparation of intravenous medicines.

Initially, each participant will provide limited demographic and nursing experience data on a paper data collection form. Some of this information will then be used to confirm eligibility and complete the online stratified randomisation process described in Section 3.

The participant will be given a printed simulated inpatient medication order and administration record for bathicillin, in the format used by their hospital. He or she will also be provided with a vial of placebo powder for reconstitution labelled as “Bathicillin 200mg”, as well as a number of other vials of placebo powder for reconstitution labelled as other simulated medicines (such as “bathymicin”) or other strengths of bathicillin. These other simulated medicines will make it possible for participants to select the wrong ampoule to make the dose, as can happen in routine practice. The participant will be asked to take any other equipment they require (such as syringes, needles, infusion fluid) from the supplies available for the preparation and administration of intravenous medicines in their clinical area.

As described in Section 3, the participant will then open their allocated IMG monograph on the data collection laptop and will be asked to prepare and administer a dose of bathicillin in accordance with

the simulated medication order, their allocated version of the IMG monograph and all relevant policies or procedures used within their hospital. They will be asked to do this exactly as they would for an actual patient. The dose will be administered to a training manikin arm located in the room in which the dose was prepared.

During these procedures, participants will be unobtrusively observed by the Chief Investigator and any preparation or administration errors noted using a structured, printed observation schedule based on best practice guidelines. Structured observation is the gold standard method in research into medication administration errors[8,21,39].

In addition, the time taken to prepare and administer the dose will be recorded on the observation schedule. The observer will start a stopwatch at the point at which the participant opens their allocated IMG monograph, and stop it when they inform the observer that they would leave the simulated patient's bedside with the infusion running. At this time, the participant will be asked to close their allocated IMG monograph file, so that blinding is maintained.

Participant feedback measures

Once the preparation and administration of bathicillin is complete, participants will complete a modified Provider Decision Process Assessment Instrument (mPDPAI) questionnaire on the data collection form[31]. This is the only validated tool for measuring health professionals' degree knowledge and uncertainty whilst making decisions[31,40]. The original PDPAI was designed to measure physicians' degree of comfort with a clinical decision[31]. It comprised of a 12-item questionnaire assessing four different dimensions: uncertainty, knowledge, value and effectiveness[31,40]. Each question was answered with a 5-point Likert scale and a Decisional Conflict Score (DCS) was calculated by summing the response. A high DCS indicated a greater degree of uncertainty about the decision. Subsequently, the PDPAI has been utilised by a variety of studies, in both its original format[40] and following modifications to its wording, number of items, response scale and language[41-44]

The psychometric properties of the original PDPAI were initially established in a group of primary and secondary care physicians[31]. Reliability was investigated by quantifying the degree of internal consistency using Cronbach's alpha, giving a result of 0.878[31]. Face validity was assessed using feedback from participants and construct validity was explored by hypothesising that there would be a negative correlation between the DCS and participants' rating of the quality of the decision and their satisfaction with it. Spearman's rank correlation coefficients were -0.58 and -0.52, respectively[31]. Subsequent studies the original or modified versions of the PDPAI also measured internal consistency, resulting in Cronbach's alpha values ranging from 0.78 to 0.82[41,45,46], indicating an acceptable degree of reliability[47].

The PDPAI has been modified for use in this current study, by removing questions 6, 8, 9 and 10 from the original instrument, as these related to concepts not relevant in this context (risk vs benefit, patient compliance and patient views/understanding). The remaining questions were reworded, to change their focus from a single decision relating to which treatment to choose, to a series of decisions relating to how to prepare and administer bathicillin. In order to investigate the psychometric properties of this modified PDPAI with the participants of this study, the previously used quality and satisfaction validation questions were similarly reworded for use in this study.

Finally, each participant will be shown both versions of the IMG monograph. They will be asked to look at both of them and record which they prefer, using a seven-point rating scale on the data collection form. This approach has been used in previous randomised trials comparing documents used in the generation of clinical guidelines.[48,49].

Debrief interview

Following completion of the observational data collection, each participant who was observed to make an IMG-related error will be invited to take part in a short debrief interview with the Chief Investigator, to provide an understanding of the types of error observed and their causes. There will be a particular focus on how errors relate to the information provided in the monograph. The critical incident technique will be used to investigate whether or not the error was related to the IMG monograph. This approach has been used before to understand the causes of medication errors by exploring the intentions, behaviours and actions of participants involved in a specific situation[16,50-52]. Participants will be asked to describe the chain of events leading up to the error, the circumstances in which it occurred, the perceived reasons for the error, and how it might have been prevented[16,50-53].

An interview schedule covering these subjects has been prepared by the Chief Investigator, based on previous relevant research and topic guides [16,50-53]. This interview schedule may evolve as data collection progresses, to ensure it adequately reflects issues raised during preceding interviews. Each interview will be audio recorded using a password protected digital recorder, and the interviewer will make field notes. To ensure confidentiality and patient safety, participants will only be invited to take part in an interview when a suitable private room is available and the participant does not have an urgent clinical task to carry out. As soon as practical, the recordings will be transferred to the University of Bath's secure research data storage facility and deleted from the digital recorder. Subsequently, the interview recordings will be transcribed by experienced transcribers employed by the University of Bath. The Chief Investigator will remove any information that could potentially be used to identify a research participant from the transcripts before subsequent analysis and reporting.

Pilot study

Prior to commencing data collection, there will be pilot observations with five participants to ensure that the data collection process works as expected. Data from the pilot will only be included in the final results if no substantial changes are made to the data collection techniques.

Video analysis to investigate observer reliability

To investigate the reliability of the observations, a proportion of the *in situ* simulations will be videoed for subsequent analysis by a second trained observer. A recent systematic review found that inter-rater reliability was only investigated in 5 of 88 articles describing the observation of medication administration errors[54]. In four of these articles, paired observations took place only during the training of observers and piloting of the study procedures[55-58]. In one study, paired observations occurred during observer training but also during data collection[59]. There were 528 paired observations of drug administrations of a total of 4271 observed doses (12.4%).

Therefore, in the current study, all five pilot observations and 10% of the main data collection observations will be videoed. The first 12 assessments (5%) will be videoed, with the remaining 12 (5%) being evenly distributed throughout the rest of the study. This distribution of videoed observations will ensure that observations are reliable before the majority of the data are collected, but also allow the on-going reliability to be quantified. During the main (non-pilot) study, if a nurse does not consent to be videoed, they will still be included in the study, but the videoed observation will be moved to the next available consenting participant.

Video recordings will be made using a small high definition camera strapped to the participant's forehead. Preliminary work shows that such a camera captures video of where the wearer is looking in sufficient detail to enable accurate observation of the details of intravenous medicine preparation and administration. Use of a camera strapped to the participant's forehead also ensures that they do not appear in the video, thus preserving their anonymity.

Missing data

As all data will be collected in a single session, techniques to promote participant retention are not necessary and it is likely that complete data will be obtained from all participants. However, should a participant choose to leave the study before completing *in situ* simulation, their data will be discounted. If a participant completes the *in situ* simulation but does not complete the subsequent secondary outcome measures, the observational data collecting will be included in the final data set, along with their mPDPAI and preference data, if complete.

Severity determination

Once the *in situ* simulation data collection is complete, the potential severity of each observed error will be determined using a validated method which is appropriate for situations where actual patient outcome is unknown, as in this study[8,9,60]. This approach has been widely used in medication errors research, including in studies of the preparation and administration of injectable medicines[23,24,32,61].

A panel of two experienced physicians (minimum of seven years' experience), three senior pharmacists (minimum of seven years' experience) and two senior nurses (ward manager or more senior, or equivalent) will be sent a brief description of each error with the monograph anonymisation process reversed and asked individually to score the potential clinical significance of each error from 0 (no harm) to 10 (death)[60].

An online survey platform (Online Surveys) will be used to collect these data. No personal data relating to the panel members will be collected via the online survey. Each panel member will be offered a £50 gift voucher in acknowledgement of their contribution.

The validity and reliability of this approach to scoring the potential significance of medication errors has been thoroughly investigated in a study in which 30 healthcare professionals (ten physicians, ten pharmacists and ten nurses) scored 50 medication errors[60]. Ten of these errors were scored twice, two weeks apart. Generalisability theory was used to investigate the reliability of this approach, finding that most of the variance between severity scores was attributable to the inherent differences between the errors. Some of the variance was attributable to the differences between individual panel members, but little was attributable to the occasion on which the error was scored or the professional background of the panel member. Further analysis suggested that a panel of four healthcare professionals (from any profession) would result in a generalisability coefficient of 0.83, which increased with the number of panel members. A generalisability coefficient of 0.8 or more is considered to represent an acceptable level of reliability[60]. In this study, the use of a panel of seven health professionals from a variety of backgrounds will therefore ensure a reliable measure of the severity of the errors observed during the *in situ* simulation.

The same study also investigated the validity of this method, by asking the panel of thirty healthcare professionals to score sixteen medication errors with known outcomes ranging from minor to severe. There was a clear relationship between the known outcome and the panel severity scores, thus establishing the validity of this method. Mean severity scores ranged from 1.1 to 2.3 for errors with a known minor outcome, from 3.3 to 6.5 for errors with a known moderate outcome and from 6.7 to 9.6 for errors with a known severe outcome[60]. The validity of this method in this study will be investigated in a similar way, by asking the panel members to score 15 actual injectable medication errors with a known outcome (five errors each with a known minor, moderate and severe outcome). These errors have been obtained from reports in the literature[62-66].

4.2 Data management

Data will be entered by the Chief Investigator and double-checked on a separate occasion.

Electronic data will be stored on the University of Bath's secure managed data storage facility. This facility is password protected to ensure security and resilience. Multiple copies are stored in more than one physical location and measures are taken to protect against corruption. Backups are taken daily and kept for three months. A 'previous versions' feature of the storage enables recovery of files.

Anonymous electronic data will be collected at participating sites on a password protected University of Bath laptop computer. Immediately after each data collection session, the latest version of the anonymous study database will be backed up to an encrypted memory stick. At the end of each day on which data are collected (or sooner if a network connection is available), these data will be copied to the University of Bath's secure managed data storage facility.

Paper data collection forms will be stored in a locked cabinet in a locked office at the University of Bath. They will be stored in this location at the first possible opportunity after each data collection session.

4.3 Data analysis

Observer reliability analysis

Each videoed observation will be independently rated by a trained observer using the same structured observation schedule as was used for the "live" observation. The inter-rater reliability between the live and video observer will be quantified by calculation of Cohen's kappa using each point of the observation schedule as a data point (error vs no error)[67]. If the marginal distributions indicate the prevalence problem (observations fall under one category of ratings (error or no error) at a much higher rate than the other), the variant of Cohen's kappa proposed by Byrt *et al*. will be used[67,68].

Cohen's kappa will be calculated after the pilot observations are completed. The main study will only commence if Cohen's kappa calculated after the pilot observations is ≥0.80[67]. If Cohen's kappa is <0.80, the live and video observers will discuss their ratings to achieve consensus and if necessary, revise the observation schedule and definitions before repeating the pilot study. This process will continue until Cohen's kappa is ≥0.80. Cohen's kappa will also be calculated after the first 5% of data collection observations and the procedure described above for the pilot study will be repeated.

Even if Cohen's kappa is ≥0.80 after the pilot study and the first 5% of data collection observations, the two observers will still discuss ratings to achieve consensus and apply these findings to the rating of subsequent observations.

Statistical analysis of observation data

Statistical analysis will be performed using SPSS, STATA, R and Microsoft Excel.

There are plausible reasons for each of the following participant characteristics modulating the effect size of both the primary and secondary outcomes:

- Participants whose first language is not English.
- Participants with <5 years' experience of administering intravenous medicines, because evidence suggests that the number of errors with which a nurse is involved decreases over the first four to six years of their nursing experience[25,36-38]. In particular, one study found that the risk of intravenous medicine administration errors decreased with each year of a nurse's experience up to six years[25].
- Participants who have previously used the national IMG on a regular basis, as they will be familiar with the layout of the "original" monograph.

Therefore, these characteristics will be considered during the analysis.

First, the data derived from the severity scoring panel will be analysed. The mean severity score allocated by the panel for each confirmed error will be calculated. The potential severity of the outcome for each error will be determined from this mean severity score, as follows:

- Mean severity score <3 = minor outcome
- Mean severity score 3-7 = moderate outcome

- Mean severity score >7 = severe outcome

The inter-rater reliability of the severity scoring panel will be investigated by the calculation of Cronbach's alpha[47]. A coefficient ≥0.70 will be considered an indicator of acceptable reliability. The validity of the severity scoring panel will be investigated by comparing the mean severity scores of the actual errors with their known outcomes (minor, moderate or severe).

Subsequently, the moderate-severe IMG-related error rate (primary outcome), the minor IMG-related error rate, and the moderate-severe and minor non-IMG-related error rates will be calculated, based on the above analysis of the severity scores. Following the approach of recent meta-analyses[8,9], each error rate will be calculated as a percentage as follows:

$$Error\ rate = \frac{Number\ of\ observations\ containing\ one\ or\ more\ errors}{Total\ number\ of\ observations} \times 100$$

Where one observation contains more than one error, it will be allocated the severity category of the most severe of the individual errors.

Each of these four error rates will then be compared between the two groups using a Chi squared test at the 5% significance level (one test for each hospital site and one for the overall data). This will be followed by a mixed effects logistic regression analysis, with hospital site as the random effect and the other characteristics as fixed effects.

Subject to the distribution of the data, the mean and standard deviation of the time taken for each group to complete the *in situ* simulation will be calculated. These will be compared using time to event analysis (depending on the distribution of the data, probably a Cox proportional hazards model), considering the data from each hospital. The overall data will also be analysed in a similar fashion, with the model incorporating hospital site as a random effect and the other characteristics as fixed effects.

Participant responses to the mPDPAI questions will be used to calculated a modified Decision Conflict Score (mDCS), following the methods described for the original PDPAI[31]. Participants responses to these questions will use a five point Likert scale ranging from strongly agree (scoring 1) to strongly disagree (scoring 5). To calculate a participant's mDCS, the Likert scores will be summed for questions 13 to 20 of the data collection tool, after reversing the scores for question 13, 14, 16 and 17. It will therefore be possible for the mDCS to range from 8 to 40, with a higher score reflecting a higher degree of uncertainty whilst preparing and administering bathicillin.

Individual participants' mDCS will be derived. Subject to the distribution of the data, linear regression will be used to analyse the effects of IMG monograph, hospital, first language, nursing experience and previous IMG experience on the mDCS score.

The psychometric properties of the mPDPAI in the study population will be investigated using the methods used in the initial development of the PDPAI[31]. Item homogeneity will be evaluated by calculating Pearson correlation coefficients between each item and a revised mDCS calculated by removing that item from the total score. Outliers will be defined as items with a correlation coefficient less than 0.2[47]. Inter-item reliability will be investigated by the calculation of Cronbach's alpha. A coefficient the range 0.70-0.90 will be considered an indicator of acceptable reliability[47].

Previously, construct validity was investigated by hypothesising that there would be a negative correlation between the DCS and participants' rating of the quality of the decision and their satisfaction with it[31]. The same hypotheses will be investigated for the mDCS by calculating Spearman's correlation coefficients between participants' mDCS and their responses to the quality and satisfaction validation questions (questions 21 and 22 in data collection tool). For analysis, the rating scale responses to the satisfaction question (question 22 in data collection tool) will be transformed into an ordinal scale ranging from 1 ("terrible") to 7 ("delighted"). Negative correlation between these variables will support the credibility of the two hypotheses outlined at the start of this paragraph and the validity of the mPDPAI.

Construct validity will be further investigated by testing two new hypotheses. The first new hypothesis is that that nurses who are more uncertain about how to prepare and administer the dose will take longer to complete this task. This will be investigated by calculating the Spearman's rank correlation coefficient between the mDCS scores and the time taken to complete the *in situ* simulation. Positive correlation between these variable will support the credibility of this first new hypothesis and the validity of the mPDPAI.

The second new hypothesis is that nurses who are more uncertain about how to prepare and administer the dose will be more likely to make one or more IMG-related errors (of any severity). This will be investigated by logistic regression between the mDCS score and the presence or absence of IMG-related errors for each participant. An odds ratio with a 95% confidence interval which does not cross 1.0 will support the credibility of this second new hypothesis and the validity of the mPDPAI.

Participant responses to the monograph preference question (question 23 in data collection tool) will be transformed into an ordinal scale ranging from 1 ("I strongly prefer guide X") to 7 ("I strongly prefer guide Y"). Subject to the distribution of the data, they will be summarised as the mean of all participants' responses and its 95% confidence interval to test the null hypothesis of no preference (mean = 4) at the 5% significance level. To investigate the possible influence of the monograph used for the simulation and hospital site on these data, the difference in mean between the two groups (and 95% confidence interval) will be calculated for each hospital and the overall data. These data will be modelled (logistic regression or Poisson regression, depending on the distribution), with the model incorporating hospital site as a random effect and the other characteristics as fixed effects.

As all data will be collected in a single session under the supervision of the Chief Investigator, full protocol adherence and complete data collection are likely to be achieved for all participants. However, should protocol non-adherence lead to a participant using the IMG version they were not allocated, data will be analysed on an as randomised (i.e. intention-to-treat) basis. Should this occur in more than 5% of participants, a per protocol analysis will also be presented for each outcome. Missing data will be ignored during the analysis, as this is likely to be minimal.

Debrief interview data analysis

A basic content analysis will be performed to quantify the proportion of errors where the participant stated that:

i. the error was related to the IMG monograph, or
ii. the error could have been prevented by a change to the monograph.

Transcripts will be independently coded for the presence or absence of the above two statements by two independent coders. Disagreements between the two coders will be resolved by discussion until consensus is achieved.

In addition, the transcript of each interview will also be subject to thematic analysis with a focus on describing the causes of the observed errors using the Yorkshire contributory factors framework[17]. Thematic analysis is an approach which allows the identification of recurrent themes and the exploration of their meaning and will be applied by following the six stages described by Braun and Clarke[69]. Nvivo software will be used during this process.

5 ETHICS AND DISSEMINATION

5.1 Research ethics approval and other regulatory review

As participants in this study are NHS staff, review by an NHS Research Ethics Committee is not required. However, a favourable opinion will be sought from the University of Bath Research Ethics Approval Committee for Health (REACH) for this protocol, informed consent forms and other relevant documents.

Approval from the Health Research Authority (HRA) will be obtained before the study commences. Before the study commences at a particular site, the Chief Investigator will ensure that the R&D department of that site has formally confirmed their capacity and capability to deliver the study.

Should any study amendments be required, the Chief Investigator will submit information to REACH and the HRA in order to seek their approval for each amendment. The Chief Investigator will then work with study sites' R&D departments so they can put the necessary arrangements in place to implement the amendment and to confirm their support for the study as amended.

5.2 Amendments

Amendments will be submitted for approval and communicated as described above. The decision to make amendments will be made and implemented by the Chief Investigator, in line with advice from the Study Advisory Group and research advisors. The sponsor will categorise amendments as substantial or non-substantial in line with their guidelines applicable at the time. Amendment history will be tracked through the use of version numbers of all documents and Appendix 2 of this protocol.

5.3 Consent

Informed consent will be obtained from all participants and recorded in writing immediately prior to their *in situ* simulation. Data collection will not commence unless consent is obtained and documented.

The Chief Investigator will work with study sites to circulate information about the study to all wards where *in situ* simulation is planned. Suitable simulation times will be agreed in advance with ward managers, who will circulate paper or electronic copies of the participant information leaflet and consent form to all nurses who will be on duty at this time at least 24 hours in advance of the simulation.

Immediately prior to a participant's simulation session, the Chief Investigator will discuss the contents of the participant information leaflet with the participant, highlighting the nature and objectives of the study and possible risks associated with participation. The participant will be given the opportunity to ask questions about any aspect of the study they do not fully understand. As participants in this study will be qualified, practising nurses, it is very likely that all potential participants will have capacity to consent. If the potential participant demonstrates the ability to retain and understand the information provided about the study, they will be deemed capable and asked to complete the consent form.

5.4 Confidentiality

All investigators must comply with the requirements of the University of Bath Research Data Policy, which is based on current national data protection requirements.

Personal information will be collected via consent forms and demographic data collection. However, demographic data will be collected anonymously. Paper forms will be returned to the University of Bath as soon as possible after completion, where they will be stored in a locked cabinet in a locked office.

The debrief interview audio recordings can also be considered personal information. They will be made using a password protected digital recorder and then transferred to the University of Bath's secure managed data storage facility as soon as a suitable secure network connection is available. They will be deleted from the digital recorder at this point. Recordings will subsequently be transcribed. Transcriptions will also be stored in a password protected folder in the University of Bath's secure managed data storage facility and will be anonymised by replacing any potentially identifiable information with an unrelated sequence of characters.

Participants will not be identifiable from the video recordings made to investigate observer reliability, as only their hands will be recorded. However, video files will be transferred to the University of Bath's secure managed data storage facility as soon as a suitable secure network connection is available and then deleted from the digital recorder.

All data will be identified using only a unique participant number. Records linking unique participant numbers with identifiable individuals will not be made.

Data will be shared with team members outside the University of Bath using the secure files.bath file sharing facility (www.bath.ac.uk/guides/access-and-share-your-work-online-using-files-bath/). Data will

be stored for ten years, in accordance with the University of Bath Research Data Policy (www.bath.ac.uk/research/data/policy/).

5.5 Declaration of Interests

The Chief Investigator has no financial or other competing interests to declare.

5.6 Access to data

Access to data will be limited to the Chief Investigator, research advisors and sponsor's representatives. Suitable anonymised data may be made available via the University of Bath Research Data Archive (https://researchdata.bath.ac.uk/).

5.7 Dissemination policy

Data arising from this study will be owned by the University of Bath. On completion of the study, data will be analysed and tabulated and a Final Study Report submitted to the NIHR. This report will be accessible via the NIHR. The Chief Investigator will have the right to publish any of the study data, subject to acknowledgement and approval of the submission by the NIHR.

Participants who on their consent form express an interest in finding out about the results of the study will be sent a copy of the final study report.

The study protocol, final study report and anonymised participant level dataset may be made publicly available via the University of Bath Research Data Archive (https://researchdata.bath.ac.uk/) at the conclusion of the study.

The author of the final study report will be the Chief Investigator. Authorship of academic publications arising from this study will be determined according to the International Committee of Medical Journal Editors criteria for defining the role of authors and contributors:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

See: www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

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7. APPENDICIES

11.1 Appendix 1 – Required documentation

- CV of Chief Investigator
- Participant information sheet
- Consent form
- Microsoft Excel data collection tool
- Structured observation schedule
- Debrief interview schedule

13.3 Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	31/1/2019	Matthew Jones	Excel data collection tool for demographics and participant feedback data changed to paper form
2	1.2	5/6/2019	Matthew Jones	Secondary outcomes description amended to make it clear that these will consider the rates of errors of all severity, not just minor errors (not a protocol change, but a clarification). Given the high prevalence of errors found in the project so far and difficulty finding suitable private space, debrief interview procedure amended to specify that only participants making IMG-

				related errors will be invited to take part in an interview, and this will only take place if a suitable private space is available and the participant does not have urgent clinical tasks to carry out. Severity panel procedure amended to remove the validation that the observation was indeed an error, as this role is better fulfilled by the video analysis. Panel voucher payment increased to £50.