**The SIMPLIFI (Single use Isothermal aMPLIfication testing for Flu Illnesses) Study**

Evaluation of a single use point of care device for the diagnosis of influenza and other respiratory pathogens in clinical upper airway samples using isothermal amplification – a feasibility study.

Study Protocol Version 1.0

Date: 08/08/2019

**Sponsor:** Imperial College London

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**Study Coordination Centre:** Imperial Clinical Respiratory Research Unit (ICRRU), Imperial College London IRAS Project ID: 266797

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**Protocol Authorised by:**

| Name & Role | Date | Signature |
|---|---|---|
| | | |

**Study Management Group:**

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**Clinical Queries:**

Clinical queries should be direct to Mirae Park, who will direct the query to the appropriate member of the study team.

**Sponsor:**

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office

Imperial College London and Imperial College Healthcare NHS Trust, Room 221, Level 2, Medical School Building, Norfolk Place, London, W2 1PG

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http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice

**Funder:**

The study is funded by the National Institute for Health Research (NIHR) Grant Scheme i4i (Grant II-LB0716-20003).

This protocol describes the Sense influenza point of care testing device and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. Any such amendments will be circulated to investigators in the study.

Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

**Study Summary:**

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| Study Title | Evaluation of a single use point of care device for the diagnosis of influenza and other respiratory pathogens in clinical upper airway samples using isothermal amplification. |
| Study Design | A prospective single centre feasibility study carried out in Accident and Emergency department of Imperial College Healthcare NHS Trust in patients presenting with influenza like illness. |
| Primary Objective | To assess the feasibility of this novel single use product for the diagnosis of influenza and other respiratory pathogens in upper airway samples at the point of care in acute clinical settings and compare the results against the conventional diagnostic methods of Polymerase |

| | |
|---|---|
| | Chain Reaction testing in the laboratory and/or rapid flu testing (Cepheid, Sunnyvale, CA, USA). |
| Secondary Objectives | To compare the results obtained in a clinical setting to the analytical study data and laboratory test on stored samples.<br><br>A further objective is to develop a bank of research samples for further testing of the device in laboratory conditions. |
| Population | Any consenting adult presenting to the Accident and Emergency department with influenza like illness or a febrile illness associated with symptoms such as cough, sore throat or rhinorrhoea, and for whom a respiratory viral screen is clinically indicated will be recruited. |
| Eligibility | Inclusion criteria:<br>Any adults ≥18 years of age who is:<br>- Able to provide written informed consent, or written informed assent by a relative or carer can be provided<br>- Recruited during initial medical assessment<br>- Able to comply with the study protocol<br><br>Exclusion criteria:<br>- Previously recruited within 28 days of the current admission<br>- Enrolment in a trial of antimicrobial therapy<br>- If patients are unable to understand verbal or written information in English, hospital translation services will be sought but not guaranteed. However, if the team member seeking consent is not satisfied that the potential recruits' English language ability is sufficient to completely understand the study protocol and requirements (despite use of hospital translation services) then they will not be recruited to the study. |
| Interventions/Procedures | One nasal swab in addition to the swab(s) (nasal, nasopharyngeal and/or throat swab) taken for standard care. |
| Follow up | N/A |

# Contents

Key words:

| |
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| Point of care (POC) |
| Influenza |
| Influenza like illness (ILI) |

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| Flu |
| Respiratory virus |
| Nasal swab |
| Nasopharyngeal swab |
| Single use |
| Diagnostics |
| Isothermal amplification |
| Accident and Emergency (A+E) department |

# 1. Introduction

## 1.1 Background

Influenza is a contagious respiratory illness that is a leading cause of acute respiratory infections and causes a continuous threat to global health, the viruses mutating and spreading in both human and animal populations. In the period from March to May 2009 a novel swine-origin influenza A (H1N1) virus emerged in Mexico and the United States (1,2). Most cases were acute and self-limiting among children and young adults (1) although the global mortality over the first 12 months has been estimated at over 200,000 respiratory deaths (3). Those with severe illness typically presented with viral pneumonitis or pneumonia, sometimes complicated by multi-organ failure.

Although influenza is a clinical diagnosis, diagnostic testing can influence clinical decisions with regards to infection prevention measures by isolation, starting anti-viral treatment and with hospital admissions or hospital discharges.

Current influenza testing can be performed by numerous methods. The gold standard is via molecular assays including rapid molecular assays and reverse transcription polymerase chain reaction (RT-PCR). Serological testing and antigen detection tests including immunofluorescence assays are other methods but the sensitivity and specificity for these tests are variable and tend to be lower than molecular testing methods (4).

In the UK, influenza testing relies on clinical suspicion and the use of respiratory viral PCR in the laboratory (5,6). This can have a turn-around time of 24-48 hours (5), and the public health control of influenza is time critical. With this in mind, point of care (POC) testing has been considered by Public Health England, as platforms with the potential to be used within 20 metres of patients and the results to be available within 10 to 90 minutes for the diagnosis of influenza have been invested in, researched and developed since the late 1990's.

Numerous devices and tests have been developed with the first generation being dependent on viral antigen testing. The second generation devices consisting of nucleic acid amplification technologies (NAAT) (4).

| | Sensitivity | Specificity |
|---|---|---|
| First generation<br>Single antigen based | 50-70% | 85-100% |
| Second generation<br>NAAT based<br>Single target (influenza A+B) | 90-99% | 95-99% |

| | | |
|---|---|---|
| Second generation<br>NAAT based<br>Multi targets | 90-99% | 95-99% |

Table from PHE (4)

The rational for this study is to assess the feasibility of a novel single use product for the diagnosis of influenza and other respiratory pathogen in patients presenting with influenza like illness (ILI).

With the results being available at the POC when patients initially seek medical attention, the aim is to assist with immediate clinical decision regarding the need for isolation due to a respiratory infections, initiation of anti-viral treatment and potential discharge plans. This feasibility study will help develop this POC diagnostic device.

### 1.2 Hypothesis

The new single use POC device will be feasible to use as a diagnostic device for influenza and other respiratory viruses in a clinical setting.

## 2. Aims and Objectives

### 2.1 Primary aims and objectives:

To assess the feasibility of this novel single use product for the diagnosis of influenza and other respiratory pathogen in upper airway samples at the POC in acute clinical settings and compare the results against the conventional diagnostic methods of PCR testing in the laboratory and or rapid flu testing (Cepheid, Sunnyvale, CA, USA).

Usability, performance and final results from the new POC device will be analysed in an acute clinical setting (in a real-life acute setting vs conventional testing). The diagnostic performance of this data will be reviewed and analysed compared to the current standard test of viral PCR results in the laboratory and/or rapid flu testing (Cepheid, Sunnyvale, CA, USA).

### 2.2 Secondary aims and objectives:

To compare the results obtained in a clinical setting to the analytical study data and laboratory test on stored samples. A further objective is to develop a bank of research samples for further testing of the device in laboratory conditions.

Sensitivity, specificity, positive predictive value and negative predictive value of the new POC device in fresh samples will be calculated and compared to the results on stored samples.

## 3. Study Design

This is a prospective single centre feasibility study carried out in an acute clinical setting, the Accident and Emergency (A+E) department of Imperial College Healthcare NHS Trust (ICHNT).

The patient will be seen in the clinical setting on a one off visit. Any adult presenting with ILI or a febrile illness associated with symptoms such as cough, sore throat or rhinorrhoea, and for whom a respiratory viral screen is clinically indicated will be recruited if they meet the eligibility criteria.

One nasal swab to be taken per patient recruited in addition to the swab(s) (nasal, nasopharyngeal or throat swab) taken for standard care. Routine sample(s) (A) to be processed for standard PCR testing in the laboratory and/or rapid flu testing (Cepheid, Sunnyvale, CA, USA) as per standard clinical work flow. Second sample (B) to be taken for evaluation under the study and either: (i) transferred to the new device buffer tube and promptly tested in a test device or (ii) if no device is available for prompt testing, add the swab to a viral storage/transport buffer tube as per standard procedures and freeze for long-term storage and later testing.

Tests on this device should be performed 'blinded', i.e. operator unaware of diagnostic standard of care result to ensure clinical decisions/reading of results are not based upon results obtained with prototype tests. The test result should not be disclosed to either the patient or the clinician. Each patient will be expected to participate for a total of 30 minutes.

As this is a feasibility study, diagnostic standard of care tests should be performed as per the clinical pathway with routine sample(s) (A) and the results of the test devices should not affect clinical decisions.

A minimum of 50 devices will be tested with fresh patient samples in a real life clinical setting. Opportunistic patient samples will be collected and banked throughout the study period. The aim will be to recruit as many patients as possible. A target of 200 patients has been set based on 1600 viral PCRs taken at ICHNT last year over the influenza period and a realistic estimate was made for the sample size for patients who may be willing to participate in the study presenting with ILI, with consideration of financial, time and resource constraints. This data will be analysed to review the feasibility for this new device.

The primary outcome will be to review the feasibility and the diagnostic accuracy for viral respiratory pathogens in this novel device using fresh patients' samples in a real-life clinical setting compared to the standard diagnostic testing of a respiratory viral PCR in the laboratory and/or rapid flu swab (Cepheid, Sunnyvale, CA, USA) using sensitivity, specificity, positive predictive value and negative predictive values.

The secondary outcome will be to review the feasibility and the diagnostic accuracy for viral respiratory pathogens in this novel device using fresh patients' samples in a real-life clinical setting compared to the laboratory settings using stored samples using sensitivity, specificity, positive predictive values and negative predictive values.

## 3.1 Study Population

Any adult ≥18 years of age presenting to the A+E department with ILI or a febrile illness associated with symptoms such as cough, sore throat or rhinorrhoea, and for whom a respiratory viral screen is clinically indicated will be recruited if they meet the inclusion criteria.

For ICHNT the A+E department may involve St Mary's Hospital and Charing Cross Hospital. The recruiting period will be estimated between 1/11/19 to 30/4/20 over this year's influenza period. The definition of the end of trial will be the last visit of the last subject.

Clinical information including patient demographics, presenting symptoms and signs, past medical history, medication lists and risk factors, will be documented and recorded.

# 4. Patient Entry and Procedures

Potential patients will be recruited from A+E department at ICHNT. The clinical research nurse or fellow will liaise closely with the A+E staff to identify any patient presenting with ILI symptoms. Cerner, an electronic based healthcare records system, can also be accessed to identify these patients presenting with ILI symptoms. The patient will be approached by the clinical research team (either the research nurse or fellow) who will explain the study and provide a patient information sheet. If the patient voluntarily agrees to participate in this study, a written consent form will be obtained. The patients will be made fully aware that they may withdraw their consent from the study at any time.

To be included in the study, patients will need to meet the criteria below.

## 4.1 Inclusion Criteria

Any adult ≥18 years of age presenting to the A+E department with ILI or a febrile illness associated with symptoms such as cough, sore throat or rhinorrhoea, and for whom a respiratory viral screen is clinically indicated and who is:

- Able to provide written informed consent, or written informed assent by a relative or carer

- Recruited during initial medical assessment

- Able to comply with the study protocol

## 4.2 Exclusion Criteria

- Previously recruited within 28 days of the current admission

- Enrolment in a trial of antimicrobial therapy

- If patients are unable to understand verbal or written information in English, hospital translation services will be sought but not guaranteed. However, if the team member seeking consent is not satisfied that the potential recruits' English language ability is sufficient to completely understand the study protocol and requirements (despite use of hospital translation services) then they will not be recruited to the study.

## 4.3 Consent

See also section 9.2. Each participant will be provided with an information sheet and a verbal description of this research study. It will be made clear that one extra sample will be required from the routine procedure they are undertaking. They will be informed that participation is voluntary. When a participant has been given adequate time to reflect upon and consider participation in this study and only when they have agreed to take part, they will be asked to read, sign and date a consent form. Given the simple nature of this study with only one extra sample required, participants will have

a minimum of 15 minutes to review the patient information sheet. During the informed consent procedure the participant will then be assessed for their understanding of the protocol and given time to ask any further questions. The idea is to recruit participants in the opportunistic window where they present with ILI and before clinical intervention such as antibiotics or starting of anti-virals.

Consent will also be for the use of the patients' results for this study.

Consent will be taken by a qualified doctor, member of the local clinical care team, a research nurse or clinical fellow. Three copies of the consent form will be made; a copy will be kept in the site research file, a copy given to the patient and a copy put into the participant's medical notes. The original consent form will be kept by the co-ordination centre in a secure manner and accessible only by authorised members of the research team. Participants will also be provided with contact details of the study co-ordination centre for future queries.

Participation in the study does not alter the clinical management that patients receive; the care of all patients will be in line with the local practice and guidelines at the participant's originating hospital and will be unaffected by this research.

# 5. Schedule of Events

## 5.1 Identification of participants

Any patient identified in A+E department with ILI, for whom a respiratory viral screen is clinically indicated, will be highlighted to the research team. Patients will follow the routine pathway of the A+E department with regards to investigations and treatment. If the patient is recruited into the study, an extra nasal swab will be taken in addition to the swab (s) required for standard care testing (nasal, nasopharyngeal or throat swab). This test will not affect the patient care. The medical notes will be reviewed for details of past illnesses, treatments and general physical examination. No follow up will be required.

## 5.2 Sample collection - Nasal swab

One nasal swab will be taken from the patient's nose in addition to the sample taken for standard of care testing. The swab will be rotated up to 5 times and held in place for 5-10 seconds.

## 5.3 Using single use point of care device

The swab should then be inserted into the single-use elution buffer tube containing the elution buffer and stirred 5 times. The swab should then be safely discarded in clinical waste. A volume of 200ul of buffer is then transferred to the sample chamber of the device using the fixed volume pipette provided. The assay should be performed according to the 'Instructions For Use' provided with the device. The device is turned on, the reaction started and results reported by turning a dial positioned on the device. The device automatically heats the sample and re-suspends lyophilised reagents contained within the device, initiating isothermal amplification. Heating and mixing are provided by the device and the result reported on the lateral flow strip contained within the device. Results are indicated by the clear presence or absence of a black line displayed on the lateral flow strip which corresponds to a specific pathogen on the device label. Results require no calibration, interpretation, or calculation. The total time to result is expected to be approximately 10 minutes. The pathogens

which will be tested in the test device include one or more of the following: influenza A, influenza B, respiratory syncytial virus, human rhinovirus/enterovirus, human metapneumovirus, parainfluenza viruses (1-4).

## 5.4 Banking samples

If no test device is available, the swab should then be inserted into a Copan UTM MINI 1ML, snapped off at the breakpoint and the tube capped. The sample should then be stored in the fridge at 4°C, or frozen at -20°C if freeze-thaw can be avoided, before transfer to long-term storage at -80°C in the lab as soon as possible and within 24 hours.

Samples that are not used immediately will be stored on-site at Imperial College Healthcare NHS Trust for the duration of the trial and transferred to Sense Biodetection ltd (Culham Science Centre, Abingdon OX14 3EB) once the trial concludes. Researchers associated with the trial will have access to the samples and associated anonymised data. These may also be used in other ethically approved research studies by Imperial College London or our collaborators in the UK and abroad. The samples and the research results will be completely anonymised and there is no way that you can be identified through the stored samples.

Storage by research team of biological material which is not “relevant material” for the purposes of the Human Tissue Act.

## 5.5 Follow Up and Data Collection

### 5.51 Participant Follow Up

Patients will not be followed up but will follow the routine clinical pathway in the A+E department.

### 5.52 Data Collection

Medical and demographic data will be collected during the study and documented on the following case report forms (CRFs).

- Baseline CRF – Including demographic information, medical history, symptoms, signs and observations at the time of recruitment
- Results CRF – Including results from the POC device, how many devices were required to obtain a results, any issues with the device, results of the standard viral PCR results, patient outcomes and use of anti-viral treatment.

Additional data will be collected where required using the following CRFs:

- Adverse Events/Serious Adverse Events CRF – refer to section 7 for details
- Withdrawal CRF – to be completed if patient withdraws consent.

This data will be collected by a clinical research fellow or research nurses using participant hospital records or from the participant directly. In addition, pseudo-anonymised test results and imaging reports maybe collected. This could include but will not be limited to X-ray reports, CT scan reports, and pathology reports.

Physical copies of personal data will be kept in a secure records room in ICRRU. This records room has a combination lock code only known to the clinical research team. This records room is further contained in a secure area of the ICRRU which requires swipe-card access.

Personal data will be kept in pseudo-anonymised form. Each participant will be given a study number with a link code which can be used to refer to the participant's information. This link code will only be available to the clinical research team on a NHS computer. Data arising from the study, for publication or dissemination will retain no link to the original participant, and participants will not be identifiable from any published or disseminated materials. Anonymised (removing the link code and removing any link to original participant data), non-identifiable, information may be shared with academic collaborators.

### 5.6 Withdrawal Criteria

Participants may withdraw from the study at any time without giving a reason. In accordance with the current Declaration of Helsinki and any other applicable regulations, withdrawal is without prejudice to the participant's current or future medical care, and the participant is not obliged to give their reasons for doing so.

The investigator, may withdraw a participant from the study at any time if, according to clinical judgment, it is deemed to be in the best interests of the participant's health and well-being.

Any withdrawal notified in person, by phone or in writing to a member of the study team shall be documented on the Withdrawal CRF and sent to the study co-ordination centre as soon as possible. Where possible, the study team member should ask the participant the following questions about the holding and use of their samples and data:

- Is the participant happy for data and samples collected to date to be used in the study analysis?
- Is the participant happy for data and samples taken to be used in future studies as specified in the information sheet and consent form?

If the study team member is unable to ask these questions, samples and data collected to date will be used as indicated in the original consent form.

## 6. ADVERSE EVENTS

### 6.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

• Results in death.

• Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

• Requires hospitalisation, or prolongation of existing inpatients' hospitalisation.

• Results in persistent or significant disability or incapacity.

• Is a congenital anomaly or birth defect.

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

### 6.2 Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator and the Study Coordinator in the first instance.

#### 6.21 Non serious AEs

All such events, whether expected or not, should be recorded according to local practice but do not need to be reported to the study centre unless they are a direct result of specific study procedures (informed consent or study sampling). AEs resulting from a research procedure should be reported to the study co-ordinator using the AE case report form.

Unexpected abnormal clinical results identified from samples taken for research purpose only will be escalated to the Chief Investigator who will follow the referral pathway.

#### 6.22 Serious AEs

An SAE form should be completed and sent to the Chief Investigator and the Study Coordinator within 24 hours. However, relapse and death due to, and hospitalisations for elective treatment of a pre-existing condition, do not need reporting as SAEs.

All SAEs should be reported where in the event was:

• 'Related', i.e. resulted from the administration of any of the research procedures; and

• 'Unexpected', i.e. an event that is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator or the Study Coordinator must also notify the Sponsor of all SAEs. Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs

Please send SAE forms to:

Email: mirae.park@nhs.net and jrco@imperial.ac.uk

Tel: 020331 25734 (Mon to Fri 09.00 – 17.00)

## 7. Statistics and Sample Analysis

### 7.1 Sample analysis

The single use POC device will only be used by the clinical research team who have been trained. A step by step guide will be provided by the manufacturers. The standard test for viral PCR swabs and/ or rapid flu swabs (Cepheid, Sunnyvale, CA, USA) will be processed according to the trusts guidelines and protocol.

### 7.2 Statistical analysis

Only suitably qualified members of the clinical research team will have access to the personal data of the study participants. Anonymised, non-identifiable, information may be shared with academic collaborators. Clinical data will be extracted from the patient or from an electronic health record system (eg Cerner). This will be recorded in a paper or an electronic case report form (CRF). On this CRF there will be an audit trail of the staff entering the data. The CRF will be transcribed to a database. Statistical analysis software will also be used to calculate sensitivity, specificity, positive predictive values and negative predictive values.

## 8. Regulatory Issues

### 8.1 Ethical Approval

The study will require ethical approval by the ethics committee and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

### 8.2 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. This study does not affect patient care; therefore, after the participant has entered the study the clinician remains free to give required treatment at any stage as per standard practice. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. Where participants seek to withdraw consent, as far as possible, permission will be requested to continue to use samples and data collected to date within the study for the purposes of follow up and data analysis. Where seeking permission for this is not possible, samples and data acquired to date will be used as indicated in the original consent form, however, no further information will be collected.

### 8.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

### 8.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

### 8.5 Sponsors

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

### 8.6 Funding

National Institute for Health Research (NIHR) has funded £1,259,355 grant number II-LB0716-20003 for a 2 year and 6 months study. Participants will not receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research. There will be no investigator payments.

### 8.7 Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

## 9. Study Management

The day-to-day management of this study will be co-ordinated through ICRRU, Imperial College Healthcare NHS Trust

## 10. Publication Policy

All publications and presentations relating to the study will be authorised by the Chief Investigator. No identifying participant information will be published. The expectation is that after analysis, data from this study will be distributed within the medical and scientific community through appropriate media subject to the customary commercial considerations of the device manufacturer. An internal report will initially be produced. Facilitated by presentations at local, national and international meetings, findings will be published widely in medical literature. There is an excellent media department at ICHNT which has considerable experience of publishing high quality research.

## 11. Public Engagement

Generating public awareness of our work within UK will actively encourage people to be more aware of the current problem with influenza and POC diagnostics. Dissemination activities to create public awareness of the scientific research will be conducted. Our group has successful track record of showcasing research at various public events such as awareness days, The Science Museum, Imperial Festival and even through various types of media including television, radio and infographics to overcome literacy/language barriers. Engaging social media is also important to create awareness. We already have institutional web portals and twitter feeds and will use these avenues to further communicate and disseminate our activities. This publicity will inform prospective end users and the public of the scope and value of research.

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