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**Study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside**

**Research study protocol**

**Version 2.1**

**08 June 2018**

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**Glossary**

**CQC** Care Quality Commission

**CTRC** Clinical Trials Research Centre

**DNA** Deoxyribonucleic acid

**EIA** Enzyme immunoassay

**GCP** Good Clinical Practice

**GP** General Practitioner

**GPP** Gastrointestinal Pathogen Panel

**HBGA** Human histo-blood group antigen

**IgA** Immunoglobulin A

**IgG** Immunoglobulin G

**IRAS** Integrated Research Approval System

**MRC** Medical Research Council

**OTU** Operational Taxonomic Units

**PCR** Polymerase chain reaction

**PHE** Public Health England

**qRT-PCR** Quantitative real-time polymerase chain reaction

**RNA** Ribonucleic acid

**SOP** Standard operating procedure

**UoL** University of Liverpool

## 1. Introduction

### 1.1. Background

Noroviruses are endemic in the human population and are recognised as the leading cause of infectious intestinal disease across all ages (1-3). Norovirus outbreaks predominate in settings in which there is high density of individuals, where mixing rates or interaction with contaminated surfaces are high, and where hygiene may potentially be compromised. Environments such as hospitals and nursing homes are important settings for noroviruses where the virus may be introduced from the community. However outbreaks in such settings, despite being linked to disease in the community, can be considered as distinct in terms of their seasonality, overwhelming predominance of a single genotype and impacts on vulnerable populations who are at particular risk of severe outcome if infected.

In healthy populations norovirus gastroenteritis is generally mild and self–limiting, but there is increasing evidence that it may lead to long term sequelae (4, 5) and contribute to excess mortality in the elderly and the immunocompromised (6-13).

Norovirus infections in hospitals and nursing homes are associated with high attack rates (median 50%, range 9%-78%) and may be protracted, with a mean outbreak duration of 16 days (range 3-44) and 19 days (range 6-92) in nursing homes and hospitals, respectively (14). Healthcare-associated outbreaks also pose a significant operational and economic burden to health systems (15-17); although norovirus infections occur all year round, winter peaks of infection coincide with other seasonal pressures on the healthcare systems (18, 19).

Noroviruses are a highly diverse group of single-stranded RNA viruses. There are two genogroups (I and II), comprising 9 and 22 genotypes, respectively (20), that are associated with disease in humans. Despite this great diversity, norovirus outbreaks in healthcare settings are caused predominantly by GII.4 strains. These viruses also are associated with more severe outcomes, even after accounting for the more vulnerable case-mix that they tend to infect in healthcare settings (21). The emergence of particular GII.4 variants correlates with periodic increases in the number of outbreaks and the overall magnitude of the annual norovirus epidemic cycle. This phenomenon is thought to be due to the emergence of antigenic variants for which there is little or no population immunity (22-26).

### 1.2. Transmission

Noroviruses are easily transmitted via the faecal-oral route through direct contact with infected individuals, contaminated food and water, and by aerosol dispersal following vomiting episodes which subsequently leads to contamination of the surrounding environment (27, 28).

Widespread environmental contamination occurs readily during outbreaks in healthcare settings, but its precise source of origin and its contribution to overall transmission remains poorly understood (29, 30). Detection of norovirus genetic material on environmental surfaces has been correlated with ongoing and recurring outbreaks in several settings, including healthcare institutions (31, 32).

High viral loads in faeces and vomitus during and after the acute phase of infection, low infectious dose and the short incubation time associated with noroviruses are the key factors associated with transmission in semi-closed environments (33, 34). Spatial proximity to a symptomatic case has been identified as an important factor for the propagation of norovirus infections (35-37). While there are both symptomatic and asymptomatic infections among patients and staff, it appears that symptomatic patients are the main drivers of transmission (36).

### 1.3. Norovirus in health and social care institutions

The factors which facilitate sustained transmission in health and social care settings are likely to be the result of a combination of the environment, behaviour patterns associated with patients, visitors and staff, the characteristics of the norovirus strains, and/or host related factors that influence susceptibility to disease (35, 38).

At present the main approaches to preventing and controlling norovirus outbreaks, common across several national guidelines include promotion of hand hygiene, patient isolation (separation of symptomatic patients) and cohorting (grouping of patients based on symptoms), staff exclusion from work, visitor restrictions, enhanced environmental cleaning and disinfection, and closures of units (39-43).

Susceptibility to norovirus infection and disease is influenced by host genetic factors and acquired immunity. Genetic resistance to norovirus infection is related to human histoblood group antigen (HBGA) type. Individuals who express HBGA on cell surfaces and in bodily fluids (secretors), are generally susceptible to a wider range of norovirus strains while non-secretor individuals tend to be significantly more resistant to norovirus infections (22, 44). However, susceptibility and resistance patterns differ according to norovirus strain (45). The ability of norovirus-specific antibodies to bind to norovirus capsid sites involved in attachment to HBGA is believed to correlate with protection (23, 26, 46-49).

Predominance of GII.4 strains may be related to both the ability of this genotype to evade herd immunity through continuous evolution, but also due to its ability to attach to a wider range of cellular host receptors that are present in the majority of the population (50).

While children have the highest incidence in the community (51), the elderly, particularly those in long term care suffer a longer duration of illness with more severe symptoms, contributing to excess mortality (6, 7). Immunosenescence, increasingly recognised as a major risk factor leading to increases in inflammation, autoimmunity, cancer, susceptibility to gastrointestinal infections, and poor response to vaccines, may be important contributory factors to this(52, 53). Other risk factors may include age associated comorbidities including use of statins (8, 54, 55), nutritional status and dysbiosis associated with ageing and long term residential care (4, 56).

### 1.4. Knowledge gaps

The total burden of norovirus disease in the elderly population in the UK is poorly defined, despite the widespread acknowledgment that the elderly, and in particular, those in long term care are worst affected by norovirus illness. There are currently no surveillance programs that can systematically or accurately quantify the levels of any cause of norovirus specific gastroenteritis among the growing aging population living in care homes. The ageing population in the UK, means that those over 65 years old are the fastest growing sector of the population, which will result in increasing pressure and demand for health care and long term residential care in the future (62). Norovirus infections are known to be more severe in this sector of the population, contributing to excess hospitalization and mortality (6, 63-66).

Furthermore, so far we do not understand the relative importance of different drivers of transmission and factors that impact on susceptibility to disease and more severe illness among this population. Norovirus infections among the elderly are associated with prolonged shedding and longer duration of symptoms (67, 68), and it has been proposed that the elderly may contribute to the emergence of new epidemic strains that spread across the population (69). At present it is not understood which sector of the population acts as the reservoir for norovirus infection, and in particular for the spread of the predominant GII-4 strains. Most healthcare associated norovirus outbreaks are among the elderly (70), and although it is generally believed that those in long term residential care contribute to the burden of norovirus disease in hospitals, the role of patient transfer from long term care facilities on the introduction of norovirus infections into hospitals and subsequent nosocomial transmission among inpatients has so far not been appropriately assessed or quantified. Understanding the role interactions between individuals and with the environment plays in transmission would substantially improve the estimation of transmission rate of norovirus from different sources of infection and within different settings, enabling the full impact of vaccination on transmission to be estimated.

### 1.5. Study overview

The knowledge gaps that have been identified relate to the burden and transmission of disease caused by norovirus. Other viral and bacterial pathogens are frequently misattributed as norovirus due to syndromic surveillance and diagnosis. Of the 276 outbreaks of gastroenteritis in care homes in Liverpool and Sefton that occurred between 1 January 2012 and 31 December 2015, only 14 had laboratory confirmation of norovirus (Public Health England, private communication). Therefore, in order to ensure that the study aims are adequately addressed, the study will include all acute gastroenteritis.

## 2. Aims and objectives

### 2.1. Aims

The aim of this project is to evaluate an enhanced surveillance system for acute gastroenteritis among the elderly in care homes. This will provide data that can then be extrapolated and used in mathematical models to calculate the burden of norovirus infections in the elderly in long-term residential care in the UK, and the potential impact of a norovirus vaccine specifically targeted to this population.

### 2.2. Objectives

1) To study the feasibility of using an enhanced acute gastroenteritis surveillance system in care homes to generate novel descriptive data regarding norovirus infection in this population

2) To quantitatively assess the impact of norovirus illness on residential care institutions

3) To generate novel data on transmission dynamics and risks, by collecting both data on the pattern of interactions within care homes and data on virus characterisation

4) To understand characteristics of norovirus disease and susceptibility to infection (viral load, shedding duration, norovirus-specific IgA antibodies, blood group and microbiota composition [diversity index]) and use this to inform transmission dynamics studies, by sampling symptomatic and non-symptomatic residents

5) To understand the risk factors associated with acquiring norovirus infection in residential care settings during a norovirus outbreak

## 3. Proposed methods

### 3.1. Study setting and location

The study will take place in care homes in North West England. Care homes are defined as places which offer accommodation and personal care for people who may not be able to live independently. This includes nursing homes which offer the same type of care but with the addition of 24-hour medical care from a qualified nurse.

The North West of England has a population of over 7 million people. Within the region there is a mixture of affluent and deprived areas, urban and rural. The study sites will be in the metropolitan boroughs of Liverpool and Sefton. The combined population of these two boroughs is 746604, of which 130458 (17.47%) are aged 65 or older (71). Within the two boroughs, there are 133 care homes currently registered with the Care Quality Commission (72).

### 3.2. Sampling frame and strategy

The sampling frame is the total number of residential care homes for the elderly in the metropolitan boroughs of Liverpool and Sefton, registered with the Care Quality Commission. The sampling strategy is a convenience sample of sites that are approached and agree to participate. We will aim to recruit four study sites prospectively.

### 3.2.1. Study site inclusion process

Potential study sites will be recruited in two ways.

**Study sites recruited prospectively**

Potential study sites which are to be included in all study components will be approached through the Liverpool Community Health Trust (LCHT). We will approach care homes after discussion with LCHT so that those approached are representative of the care homes in the sampling frame (e.g. in size and complexity).

**Study sites recruited reactively**

Potential study sites within the sampling frame will report to the Public Health England Health Protection Team that they are experiencing an outbreak of gastroenteritis (as required by The Health and Social Care Act 2008). If this reported outbreak meets the definition in Section 3.3.3., PHE will inform the study team who will contact the study site to ask them to participate. Two members of the study team are substantive employees of PHE; their job roles entail surveillance of infectious disease outbreaks and they will therefore be informed of relevant outbreaks. Potential study sites which are reactively recruited will be asked to participate in the study components outlined in Sections 3.3.2., 3.3.4., 3.3.6. and 3.3.7.

Care homes which are approached by the study team and agree to participate will be included in the study. Studies recruited both prospectively and reactively will have background information collected on the type of residents, structure, capacity and staffing at the care home. This background study site information will be collected using a paper questionnaire (Appendix 1.1) when the study site is first recruited.

Please see below for a table showing the study components that will take place at study sites recruited prospectively and reactively.

|  |  |  |
| --- | --- | --- |
|  | Site recruitment | |
| Study component | **Prospective** | **Reactive** |
| 3.3.1. Enhanced surveillance system | X |  |
| 3.3.2. Pathogen testing | X | X |
| 3.3.3. Individual norovirus risk factor study | X | X |
| 3.3.4. Microbiota as a risk factor for norovirus infection and/or disease. | X | X |
| 3.3.5. Transmission dynamics study | X |  |
| 3.3.6. Norovirus outbreak risk factors | X | X |
| 3.3.7. Quantitative assessment of the impact of norovirus outbreaks | X | X |

### 3.3. Study components

After a care home has been approached and agreed to take part in the study, potential participants will be able to consent to take part in the study. Only potential participants aged 18 or over will be eligible to take part. The consent process is covered in full in Section 5.2. When consent has been obtained from a study participant, a member of the study team will complete a short questionnaire (Appendix 1.2) to capture essential demographic details for each participant.

### 3.3.1. Enhanced surveillance system

The enhanced surveillance system will have the following characteristics.

**Data collection:**

* Questionnaire recording information on current numbers of residents and staffing levels of the site
* Individual reporting of cases including onset date, medical history, duration of symptoms, complications, hospitalisation, outcome (e.g. death).
* Faecal samples will be obtained for symptomatic participants in each home to determine whether the illness is caused by norovirus or another gastrointestinal pathogen.

**Method and frequency of data collection:**

* Current numbers of residents and staffing levels will be collected using a questionnaire (Appendix 1.3), filled in by a member of staff in conjunction with a research nurse on the first Monday of each month.
* Individual case reports will be collected using a questionnaire (Appendix 1.4), filled in by a member of staff on the same day as the faecal sample is collected, then checked and collected by a research nurse on the first Monday of each month.
* Each case will have a stool sample collected for each episode of illness, as soon as possible after onset of illness.

**Study population:**

The study population will be residents and staff at study sites who have provided informed consent.

**Case definitions:**

Cases are defined as persons in the study population with the following:

a) Vomiting -Two or more episodes of vomiting in a 24 hour period OR

b) Diarrhoea -Three or more loose stools in a 24-hour period OR

c) Vomiting AND Diarrhoea – one or more episodes of BOTH symptoms in a 24-hour period

Confirmed cases will be defined as:

d) Cases with a positive laboratory diagnosis of an infectious cause

Causes of diarrhoea and vomiting should be believed to be infectious. Non-infectious causes, which are not to be counted, would include: long standing diarrhoea associated with disability or incontinence, ingestion of laxative drugs.

**The information from the enhanced surveillance system will lead to the following outcomes:**

* Inform the sample size calculation for a national enhanced surveillance system
* The burden of norovirus disease in this setting to be estimated
* Individual and institutional risk factors associated with incidence to be calculated
* The development of geospatial models to correlate incidence in care homes with other indicators of disease such as gastroenteritis consultation rates in primary care
* Extrapolation will make it possible to generate national estimates for burden of disease in residential care homes.

### 3.3.2. Pathogen testing

Stool samples will be collected for cases (as defined in Section 3.3.1), following the guidance in Appendix 2.1. Study research nurses will train care home staff on following this guidance. The specimen request form in Appendix 1.5 will be completed and the sample and request form will be submitted to a diagnostic virology laboratory to be tested for gastrointestinal pathogens. Samples will be posted using approved containers for the transport of diagnostic specimens.

Samples that would have been collected as part of routine clinical care will be sent to the laboratory at The Royal Liverpool University Hospital as per the current guidance. Samples collected for the study which are not part of routine clinical care will also be sent to the laboratory in The Royal Liverpool University Hospital.

Diagnostic tests will be batched, and results reported to the study team. Samples will be tested using the Luminex xTAG® Gastrointestinal Pathogen Panel which tests for the following pathogens:

Adenovirus 40/41

Rotavirus A

Norovirus GI/GII

Sapovirus\*\*

*Clostridium difficile* A/B

*Salmonella*

*Shigella*

*Campylobacter (C. jejuni, C. coli, C. pari)*

*Escherichia coli* O157

Enterotoxigenic *E. coli* (ETEC) LT/ST

*Yersina enterocolitica*

*Vibrio cholerae*

Shiga-like Toxin-producing *E. coli* (STEC) stx 1/stx 2

*Giardia lamblia*

*Cryptosporidium*

*Entamoeba histolytica*

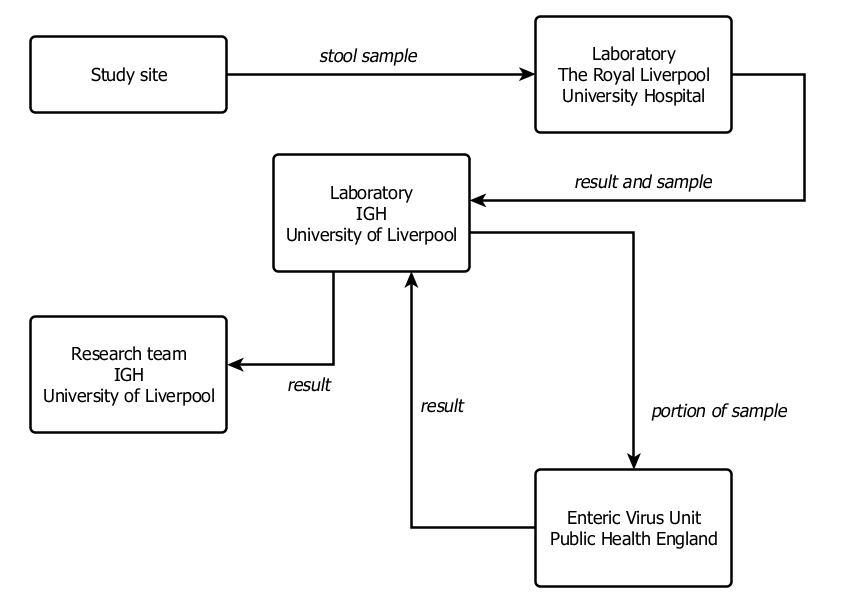
\*\* This assay has been developed for the Luminex MAGPIX® instruments but is not part of the approved Luminex xTAG® GPP

Positive results will be reported to the study team for research purposes only. The operation of this study will not interfere with public health action.

Norovirus positive samples will then be sent to UoL for subsequent investigations (see section 3.3.3 and 3.3.4). Samples positive for other viral pathogens will be sent to UoL, along with samples negative for all pathogens on Luminex. All stool samples will be stored at UoL for further research beyond this proposal.

A portion of each virus positive sample will be sent from UoL to the Enteric Virus Unit, Public Health England for genotyping and further characterisation. This work will not be conducted in real-time and will not lead to public health action.

**Diagram illustrating the operation of the pathogen testing study component**



### 3.3.3. Individual norovirus risk factor study

Cases are defined in Section 3.3.1. For each case with a norovirus positive laboratory result, where feasible, sequential stool samples will be taken at three time points (from onset): day 0-3, day 6-8 and day 12-15. Each stool sample will be taken following the guidelines in Appendix 2.1.

Sequential stool samples from norovirus positive participants will be sent to the laboratory at The Royal Liverpool University Hospital. They will be clearly marked as part of the study and not tested at the laboratory of The Royal Liverpool University Hospital. They will be collected from this laboratory and transported to UoL by a member of the study team. When at UoL, in each sample, viral load will be measured by qRT-PCR.

**Blood groups**

One of the other components for understanding susceptibility to norovirus infection is the role of blood group type and secretor status. For the purpose of testing for blood group, all participants enrolled prospectively in the enhanced surveillance will be asked to provide a sample of saliva. Samples will be taken by research nurses (saliva sampling guidance in Appendix 2.2) within a month of consent being obtained, and transported to UoL for investigation. All saliva samples will be stored at UoL for further research beyond this proposal.

**Norovirus specific antibodies:**

Norovirus reinfections are associated with an increase in cross-reactive antibodies in blood. There is currently no defined correlate of protection for norovirus infection or disease. We will conduct exploratory work in order to assess whether the presence of norovirus specific IgA in stool correlates with recovery from norovirus symptoms, and resistance to infection and/or symptoms. In addition we will investigate the potential correlation between norovirus-specific secretory (IgA) antibodies present in stool and in saliva.

Laboratory analysis that will be conducted at UoL:

* Stool samples will be tested using a norovirus-specific qRT-PCR that includes appropriate standards and controls, for calculation of viral loads in cases during acute and convalescent phase.
* EIA for the detection of blood group antigens in saliva
* PCR for determining secretor or non-secretor status from DNA obtained from the saliva samples
* EIA for the detection of norovirus-specific IgA and IgG in saliva. Results will be standardised measuring total IgA
* Stool samples will be tested by EIA in order to investigate the presence of norovirus-specific copro IgA antibodies (assays in development)

### 3.3.4. Microbiota as a risk factor for norovirus infection and/or disease.

Understanding of the susceptibility and immunity to norovirus infection and disease is incomplete and recent studies highlight the potential impact of the gut microbiota on norovirus infection (73). It is now recognised that that microbiota composition changes significantly with age (74); a decrease of bifidobacteria, which are thought to play an immune-modulatory role and represent important components of a “healthy” gut microbiota, is known to be associated with the aging process.

Studies have shown that among the elderly, the microbiota associated with those in long-term care is less diverse than among those that remain in the community, and that the loss of the “community”-like microbiota is associated with ill health (75).

Other healthcare associated infections, such as *C.difficile* diarrhoea, are associated with altered microbiota composition characterised by a loss of diversity (76), and repopulation of the gut environment with “healthy” microbiota can reverse chronic *C.difficile* diarrhoea (77, 78).

We hypothesise that the gut microbiome is likely to influence and determine the outcome of norovirus infections. This hypothesis is supported by the recent findings that norovirus can bind to HBGA-like molecules present in certain gut bacteria (73) and that gut flora directly impacts on infectivity and pathogenicity of viruses (79) by facilitating entry and infection through direct virus-bacteria interactions.

**Study inclusion criteria**

***Sites recruited prospectively***

All participants enrolled prospectively in the enhanced surveillance will be asked to provide a stool sample at the beginning of the study. Samples will be taken by research nurses (stool sampling guidance in Appendix 2.1) within a month of consent being obtained, and transported to UoL for investigation.

If study participants test positive for norovirus and provide a sequential stool sample, as detailed in study component 3.3.3., when this sample arrives at UoL for investigation it will also be used for microbiota investigations, in addition to the baseline sample.

***Sites recruited reactively***

At those sites which are recruited reactively (as defined in Section 3.2.1.) due to outbreaks of gastroenteritis, consent will be obtained from participants. All participants will be asked to provide a stool sample within a week of consent being obtained. Samples will be taken by research nurses (stool sampling guidance in Appendix 2.1) and transported to UoL for investigation.

**Microbiota analysis**

Stool samples arriving at UoL for microbiota analysis will have norovirus viral load measured by qRT-PCR. Stool samples arriving for microbiota analysis will include all those taken at study inclusion from participants at sites recruited prospectively and reactively, along with norovirus positive samples from Section 3.3.2. and sequential samples taken from Section 3.3.3.

Samples for microbiota analysis will be stored frozen for a maximum of 2 weeks prior to DNA extraction. Samples will be treated by bead beating and lysozyme prior to DNA extraction using a commercially available extraction kit. We will store two aliquots of each stool samples at -80oC, adding nucleic acid stabilising buffer to one of them. Stool DNA extraction will be conducted from the aliquots in stabilising buffer, in batches, once or twice a month. Stored stool aliquots will allow for additional studies, including metabolomic and transcriptomic analysis, subject to additional funding.

DNA samples will undergo metataxonomic analysis with 16S rDNA in the first instance. An aliquot of DNA will be stored for further metagenomic analysis, subject to obtaining additional funding. The 16S rDNA PCR strategy will use a nested dual index protocol to amplify and barcode the variable V3 - V4 region (319f - 5' ACTCCTACGGGAGGCAGCAG 3’ & 806r - 5' GGACTACHVGGGTWTCTAAT 3’) resulting in ~469 bp PCR product (80). Then barcoded 16s PCR products will be multiplexed and run in batches of up to 96 on the MiSeq to produce 2 x 300 bp reads.

Sequences generated on MiSeq will undergo a validated error correction protocol. We will trim the start and end of the reads based on quality scores using a tool such as Sickle (<https://github.com/najoshi/sickle>), error correction with BayesHammer (81) followed by overlapping reads with PANDAseq (82) with a minimum overlap of 10 bp for V3/V4 reads. These corrected and overlapped reads will then be analysed with QIIME (83). USEARCH will be run using *de novo* and open reference OTU clustering methods, and *de novo* chimera detection conducted with software such as UCHIME. Taxonomy will be assigned to OTUs using the naïve Bayesian RDP Classifier using both the SILVA and GREENGENES taxonomic databases.

### 3.3.5. Transmission dynamics study

We will quantify potential transmission paths into and within care homes using a survey instrument which has previously proved successful in characterizing interaction patterns in a US school study of influenza and other settings (84-87). Data will be collected using low-power radio-frequency devices, in order to assess contact and activity patterns within the care home with the aim of characterizing interaction networks, weighted by duration, among residents, staff and visitors.

**Study population**

Participants at care homes enrolled in study component 3.3.1. and visitors to those homes on the days of data collection.

**Study periods**

Four 24 hour periods will be chosen for the transmission dynamics study. The 24 hour periods selected will be a convenience sample based on study team availability and study site access.

**Study data collection**

Interactions between individuals will be quantified using an established method: electronic proximity sensors, called motes, which are worn by or location next to participants and detect the nearby presence of other motes. The age, gender and role of individual in the care home will be collected.

**Proximity Detecting Motes**

We will use proximity detecting motes, small electronic data-logging devices which use weak radio signals to detect when they are within range of another study mote, and which log these instances. See Figure one for an example picture of a mote. Participants will be asked to keep these motes in close proximity for the 24 period. Depending on the level of mobility of each participant, they can either be worn around the neck (enclosed in a pouch and strung on a lanyard) if the participant is walking, tied to a chair if the participant is in a stationary or mobile chair or placed on a bed-side table if the participant is in bed. The motes transmit a signal every 20 seconds and listen for other motes’ signals. Whenever a mote detects another mote, it records its unique mote ID, the current time, and the radio signal strength to approximate distance to the other mote.

Figure 1: Example of a mote



**Study process**

At the start of the chosen 24 hour study period, one of the study team will visit the care home. They will assign motes to all the participants who have consented. The member of the study team will fill in a short form (Appendix 1.6) to capture basic demographic details, information on the person’s role within the home and the number of the mote they have been assigned.

A member of the study team will remain at the site during the hours the care home is open to the public in that 24 hour period and will seek to include any visitor to the care home in the transmission study. Visitors will be given the visitor information form (Appendix 3.2) and will be able to ask the study team member any questions. After considering this information, the visitor will be asked to sign the visitor consent form (Appendix 3.3). If they do, the study team member will assign them a mote and complete the information form (Appendix 1.6). The mote will be returned when the visitor exits the study site. If they do not consent to take part, the only information that will be recorded is that a person visited.

**Data analysis**

Data will be pseudoanonymised before analysis. We will measure continuous, uninterrupted interactions between participants. We will sum the total durations of interactions over each 24 hour period and create participant contact networks with weights proportional to the total number of mutual interactions. We will use simulation modelling, point process models and network analysis to relate infection attack rates and dynamics to measured interaction patterns. We will test the hypotheses that the risk of infection is associated linearly with interaction rates and that the proximity of cases will be associated with infection risk. We will also explore how spatio-temporal proximity relates to infection risk using a range of plausible statistical models and suitable penalising criteria (Akaike Information Criterion).

### 3.3.6. Norovirus outbreak risk factors

One of the objectives of this study is to understand the risk factors associated with acquiring norovirus infection in care homes during a norovirus outbreak. When outbreaks (as defined below) are detected at study sites, the local Public Health England Health Protection Team will be informed (as required by The Health and Social Care Act 2008).

The population of a study site reactively recruited into the study due to the report of an outbreak of gastroenteritis forms a cohort which we will use for a study to investigate risk factors associated with infection. A member of the study team will administer the norovirus exposure questionnaire (Appendix 1.7). This questionnaire covers demographic, illness and medication information, along with food and drink history and information on time spent in different areas of the study site.

**Outbreak definition**

An outbreak will be defined as:

* Two or more cases (as defined in Section 3.3.1.) which occur in an institution, with onset of illness within 5 days. Cases must be study participants at the institution at the time of the incident.

An outbreak will be considered over if no new cases are ascertained for seven days.

An outbreak-free period will be defined as:

* A period of time ending three weeks before an outbreak is declared and beginning three weeks after an outbreak is considered over in an institution.

**Null hypothesis**

The null hypothesis will be that risk factors have a similar distribution in cases and non-cases.

Exposures in cases and controls will be compared using both univariable and multivariable analyses. This information will be used to assist in controlling the outbreak where possible, and also to inform wider strategies for preventing norovirus outbreaks in these settings.

### 3.3.7. Quantitative assessment of the impact of norovirus outbreaks

Research nurses will work with institutions participating in the surveillance to collect detailed information on the costs and operational disruption resulting from norovirus outbreaks. Data collected will include the symptoms of ill staff, the days of work lost, the need for additional staff (bank or agency) and additional cleaning (Appendix 1.8). Operational impact data collected will include isolation of residents, transfers to health care facilities, blocking/delays on places to new residents.

**Null hypothesis**

The null hypothesis will be that norovirus outbreaks do not have an impact on the resource usage of care homes.

A case-crossover approach will be used to compare resource usage and operational efficiency in residential institutions during outbreak periods and outbreak-free periods. Data will be collected for the whole period when an outbreak is occurring. The increased resource usage during outbreaks will be measured by comparing periods when outbreaks are occurring with periods when there is not an outbreak occurring. Measurement in outbreak free periods will take place three weeks after the end of outbreaks so that activity will resettle to normal levels.

### 3.4. Study data

### 3.4.1. Information collected

**Study site information**

For each study site, essential background information will be collected on the type of residents, structure, capacity and staffing at the care home (Appendix 1.1). Capacity and staffing information will be collected for each site on a bi-monthly basis (Appendix 1.3).

**Study participant information**

For each participant who gives informed consent, essential demographic data will be collected, along with date of entry to the study site (Appendix 1.2).

Patient level case data will be recorded for each person meeting the case definition (Appendix 1.4). In addition, sample results will be recorded for each case, with strain typing data for confirmed cases. For each sequential sample tested, the sample results will be collected. During outbreaks, all study participants in the care home will be asked to complete a norovirus exposure questionnaire (Appendix 1.7). For those participants included in the transmission study, information on study participants will be collected (Appendix 1.6), along with information collected using the motes.

**Outbreak information**

For each site in each outbreak, data on the time periods of each outbreak, and specified non-outbreak periods will be collected. For these outbreak and non-outbreak periods, operational information will be recorded (Appendix 1.8).

For a complete list of data items collected, please see Appendix 1.9.

### 3.4.2. Study data flow

The study data flows are depicted in the two figures below. The data flows for study sites recruited prospectively and reactively are shown separately. The legend describing each category of data item is shown below:

a1) Background information for each study site (Appendix 1.1)

a2) Participant demographic information (Appendix 1.2)

b) Capacity and staffing information for each study site (Appendix 1.3)

c) Individual case reports (Appendix 1.4)

d1) Stool samples for each case, routine

d2) Stool samples for each case, study

e) Sequential stool samples from norovirus positive cases

f) Saliva sample for testing blood group

g) Stool sample for microbiota analysis

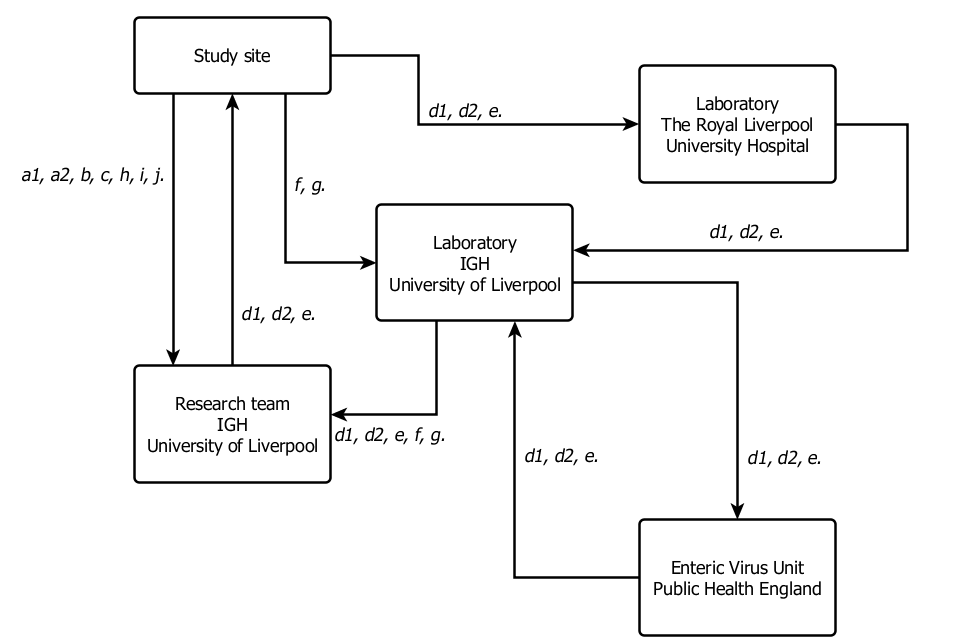
h) Transmission dynamics study data collection

i) Norovirus exposure questionnaire (Appendix 1.7)

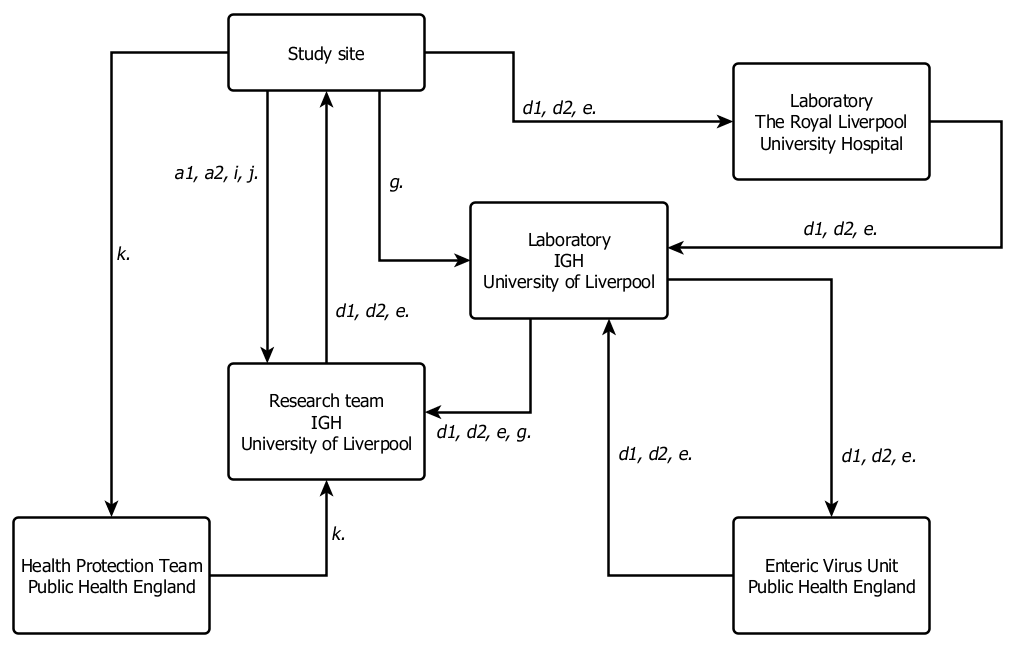
j) Quantitative impact of norovirus outbreaks questionnaire (Appendix 1.8)

k) Report of gastroenteritis outbreak

**Data flow for a study site recruited prospectively**



**Data flow for a study site recruited reactively**



### 3.5. Study management

The study will be managed by the study team with clear responsibilities for the implementation and delivery of the different aspects. Study protocols, including forms and databases for data collection and storage, laboratory standard operating procedures, including quality control and quality assurance programmes, and analytical plans will be jointly drafted and approved by all collaborators before implementation. A common training programme will be developed for research nurses and staff of study sites. The team of investigators will communicate regularly by monthly group teleconferences and quarterly project steering group meetings to be held in Liverpool. Study progress and any potential issues or deviations from protocols will be monitored in monthly meetings.

**Pseudonymisation of data**

Each participant will be assigned a unique participant ID. This ID will be randomly generated and assigned at the point that consent/assent is received. This will link data across the study (questionnaire datasets to laboratory datasets). We will not retain names, dates of birth except for reporting laboratory results, as would be done as part of routine clinical practice.

**Managing, storing and curating data**

Study data will be kept centrally within the university office on password-protected computers and access will be limited to key project staff. Data will be backed-up regularly at UoL. The UoL SOPs related to data entry and management, and data safety and privacy guidelines, will be followed.

Data and documentation at the UoL is managed, stored and curated in keeping with the University’s Information Security policy, which defines the preservation of confidentiality, integrity and availability and is informed by the principles set out in IS0 27001. All UoL computer-based information assets are stored on server systems operated by the Computing Services Department (UoL). The data storage of these systems is resilient to failures; it is backed up on a daily basis to systems also held in secure locations.

The participant ID will be used to link study datasets; a database containing non-pseudonymised participant information will be held in a separate password-protected database. Physical copies of forms containing non-pseudonymised participant information will be held in a securely locked cupboard at the following address:

The Farr Institute@HeRC

University of Liverpool

2nd Floor, Block F

Waterhouse Buildings

1-5 Brownlow Street

Liverpool

L69 3GL

Physical copies of forms containing pseudonymised data will be stored at the same address in a separate locked cupboard.

Data produced by the project will contain clinical and laboratory information, which will be handled according to UoL institutional policies outlined above and in line with MRC data management principles. All electronic files will submit to local file naming conventions and metadata will be associated where appropriate. The research team will hold the database linking participant identifiers and participant IDs on a password protected database at a secure location at the University of Liverpool. Study data will be held on password protected databases using a variety of formats including Access and SQL. For most data types, standard file formats will be used (e.g. text, Excel, Word, Access files) and data storage requirements will be manageable through centralized file servers.

### 3.6. Data analysis outline

**3.3.1. Enhanced surveillance system**

We will describe the characteristics of the surveillance system and the epidemiology of cases captured using it. We will calculate incidence rates for person-time at risk in each study site and for the study in total. We will compare the burden of norovirus, viral gastroenteritis of another cause and gastroenteritis of an unknown cause. We will describe the duration and severity of illness.

**3.3.2. Pathogen testing**

We will describe the proportion positive for norovirus and for other infectious causes of acute gastroenteritis. We will describe the sequencing results of norovirus positive samples over time, by study site and in relation to the results of the enhanced surveillance system.

**3.3.3. Individual norovirus risk factor study**

We will compare proportion and level of cases with viral shedding over time. We will categorise study participants by blood group category.

**3.3.4. Study of the microbiota as a risk factor for norovirus infection and/or disease.**

Estimates of within-sample species richness (number of OTUs) and diversity (Shannon index) at multiple rarefaction depths will be compared between cases and controls, and between samples obtained from cases during the acute and convalescent phases, using Student’s t test.

Weighted and unweighted Unifrac will be used to measure distances in microbiota composition between these groups. These results will be visualised using principal coordinates analyses and statistically significant clusters identified using *adonis.* Random Forests regression will be used to identify OTUs that distinguish norovirus cases and diarrhoeal or asymptomatic controls and between samples obtained from cases during the acute and convalescent phases.

**3.3.5. Transmission dynamics study**

We will analyse network properties (degree, strength, density) in order to assess the overall connectivity of the network. We will compare between contact networks in outbreak and non-outbreaks and between contact networks in different study sites.

**3.3.6. Norovirus outbreak risk factors**

We will compare patient characteristics and exposure histories between cases and non-cases. We will investigate differences using univariable and multivariable analyses.

**3.3.7. Quantitative assessment of the impact of norovirus outbreaks on care facilities**

We will use a case-crossover approach to compare resource usage and operational efficiency in residential institutions during outbreak periods and outbreak-free periods.

### 3.7. Bias and Limitations

This study includes participants from geographically clustered study sites. It may be that care homes selected as study sites systematically differ from other care homes both in the United Kingdom and other countries in aspects such as the demography, socio-economic status and level of morbidity of residents. The potential limitation is that any findings would be internally valid, but not generalisable to other populations.

One potential limitation is that due to the unpredictable nature of infectious disease outbreaks, there is a possibility that the study sites included in all components in the study will observe few cases and outbreak, meaning that these components will have reduced power to detect differences between groups. To address this, our protocol includes the possibility of contacting sites with a reported outbreak, and if this reported outbreak meets the definition in Section 3.3.5., the study team will try to include the study site in the study components outlined in Sections 3.3.2., 3.3.6. and 3.3.7.

Several study components include the comparison of information from outbreak and non-outbreak periods. It would be infeasible to blind the persons collecting information as to which period the study site is in. There is therefore a risk of ascertainment bias as information collected during outbreak periods may be systematically different to that collected during non-outbreak periods. We will take steps to negate this bias by rigorous training of persons involved in the study.

## 4. Adverse events

**Risks to study subjects**

Stool and saliva sampling techniques are non-invasive and minimal adverse events are expected from these procedures. The primary adverse effects of the study relate to discomfort and distress of obtaining these samples. The motes used for Section 3.3.5 use a very low power radio frequency emitter, the only minimal risk could come from the lanyard used to attach the mote.

**Risks to investigators**

Research nurses obtaining clinical samples, and laboratory staff processing clinical samples are potentially at risk from gastrointestinal pathogens in the samples. Several of the study components involve study staff entering a study site during an outbreak period, potentially exposing them to infectious agents in the environment.

**Adverse event mitigation**

To mitigate the risk of study subjects becoming entangled with the mote lanyard we will train the study staff for this study component. This training will ensure that they risk assess each study subject and minimise the risk of entanglement.

To mitigate the risks to investigators, they will be trained in the correct infection prevention and control procedures. If correct procedures are adhered to, the risk of infection is very low and the consequence would be a self-limiting illness.

**Reporting of adverse events**

All adverse events related to study procedures should be reported. The Chief Investigator should be contacted within 24 hours of the investigator becoming aware. Any questions regarding adverse event reporting should be directed towards the Chief Investigator in the first instance.

## 5. Regulatory Issues

### 5.1. Ethics Approval

The Chief Investigator has applied for approval from the Integrated Research Approval System (IRAS). 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.

### 5.2. Consent

The procedure for informed consent will be as follows. The registered manager at each study site will be provided with training so that they are able to comply with the Mental Capacity Act 2005. The registered manager at each study site will be asked to indicate which potential participants have capacity to consent. Those with capacity to consent will be given the participant information leaflet (Appendix 3.4 for residents, Appendix 3.5 for staff) and the participant letter of invitation (Appendix 3.7) by the study site staff. For those without the capacity to consent, the study site staff will identify the nominated person who makes decision on behalf of the person without capacity to consent. The study site staff will consult with the study team to ensure that these nominated persons fit the criteria described in Section 32 of the Mental Capacity Act 2005. The nominated person will be sent the appropriate participant information leaflet (Appendix 3.6), the nominated person assent form (Appendix 3.9) and the nominated person letter of information (Appendix 4.0). These materials will handed out or posted by the study site, in pre-paid envelopes which will also include a stamped and addressed envelope for nominated persons to post completed forms back to the study site.

Information describing the study aims, procedures, potential risks and benefits will be contained in the appropriate participant information leaflets (Appendices 3.4, 3.5, 3.6). For those participants at study sites which will be enrolled in Section 3.2.1., a question and answer session will be held at the study site by one of the study team. Both parts of this informed consent process (written and verbal information) will be delivered in English.

Questions from potential participants and nominated persons will be encouraged and answered fully by research nurses. Efforts will be taken, within the physical limitations of the study sites, to ensure the consent process is undertaken in an appropriately private environment. For all participants and nominated persons, the date and time that information is provided will be noted. The absolute minimum time given to potential participants and nominated persons to consider participation will be 24 hours.

Potential participants and nominated persons who agree to participate will sign a form which will make clear the entirely voluntary nature of participation, stating specifically that they can refuse, that they can withdraw from the study at any time, and that non-participation or withdrawal will not impact on any part of the participant’s healthcare. For potential participants with capacity to consent, this will be the study consent form (Appendix 3.1). For nominated persons acting on behalf of potential participant without capacity, this will be the study assent form (Appendix 3.9). Research nurses will also sign the consent and assent forms, to confirm the study has been fully explained. The consent/assent forms will be duplicate carbonless-copy paper: a copy will be retained by the study team. A copy of the study information sheet and the consent/assent form will be retained by the participant or nominated person.

Once informed consent is received, the participant’s GP will be sent a letter notifying them of the fact and explaining the nature of the study (Appendix 3.8).

**Obtaining consent from participants joining after study site recruitment**

Potential participants who join a study site after the site is first recruited will be offered the opportunity to join the study. The site will have copies of the participant information leaflet (Appendix 3.4), the participant letter of invitation (Appendix 3.7), the participant consent form (Appendix 3.1) and the nominated person assent form (Appendix 3.9). The study site will be asked to give these materials to new potential participants, or to the nominated person who makes decision on behalf of a person without capacity to consent. Each study site will be visited each week by a member of the study team, to ask whether any new participants have joined the study site and to countersign and collect consent/assent forms.

**Identifying participants who are no longer permanently associated with the study site**

A study team member will visit the study site each week. During this visit, they will record those participants who are no longer permanently associated with the study site. The date at which they left the study site will be recorded.

**Reviewing consent status**

Should the consent status of any person at a participant need to be reviewed, a member of the study team can be reached using contact details given in the participant information leaflets (Appendices 3.4, 3.5, 3.6).

**Consent process for visitors in the transmission dynamics study component**

As specified in component 3.2.5., visitors will be given the visitor information form (Appendix 3.2) and will be able to ask the study team member any questions. After considering this information, the visitor will be asked to sign the visitor consent form (Appendix 3.3). If they do, the study team member will assign them a mote and complete the information form (Appendix 1.6). If they do not consent to take part, the only information that will be recorded is that a person visited, the time of arrival and time of departure.

### 5.3. Participant involvement

**Participants at sites enrolled prospectively:**

*After consenting to take part in the study*

* Will have their demographic information recorded using the participant demographic information questionnaire (Appendix 1.2)
* Will be asked to submit a stool sample for microbiota analysis
* Will be asked to submit a saliva sample for testing blood group
* Will be asked to take part in the transmission dynamic study

*If they become ill and meet the case definition*

* Will be asked to submit a stool sample for pathogen testing
* Will be asked to submit two additional stool samples if they are positive for norovirus in the initial one

*If there is an outbreak at the care home that meets the outbreak definition*

* Will be asked to assist a member of the study team in completing the norovirus exposure questionnaire

**Participants at sites enrolled reactively:**

*After consenting to take part in the study*

* Will have their demographic information recorded using the participant demographic information questionnaire (Appendix 1.2)
* Will be asked to submit a stool sample for microbiota analysis
* Will be asked to submit a saliva sample for testing blood group

*If they become ill and meet the case definition*

* Will be asked to submit a stool sample for pathogen testing
* Will be asked to submit two additional stool samples if they are positive for norovirus in the initial one

*If the outbreak at the care home meets the outbreak definition*

* Will be asked to assist a member of the study team in completing the norovirus exposure questionnaire

### 5.4. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and will abide by the Data Protection Act.

**Formal information/data security standards**

Data will be handled according to the University of Liverpool’s information security policy which is informed by the principles set out in IS0 27001, which can be summarised as the preservation of confidentiality, integrity and availability. The following principles underpin this policy:

• Information will be protected in line with relevant laws and University policies, particularly those relating to data protection and freedom of information.

• Information should be available to all who have a legitimate need for it.

• Information must be classified according to an appropriate level of availability: public, open (within the University), confidential, strictly confidential or secret.

• Integrity of information must be maintained; information must be accurate, complete, timely and consistent with other information.

• All members of the University who have access to information have a responsibility to handle it appropriately, according to its classification.

• Nominated University staff is responsible for ensuring that appropriate procedures and systems for the processing and holding of information are in place and are effective.

• Information will be protected against unauthorised access.

• Compliance with this policy is compulsory for all staff and students making use of University information. Breaches of information security controls must be reported to, and will be investigated by, the Information Security Officer.

**Main risks to data security**

UoL data will be stored in compliance with the appropriate Standard Operating Procedures used by the Clinical Trials Research Centre (CTRC). Secure storage and processing of personal data and data access control – Compliant use of CTRC standard operating procedures ensures data storage and processing integrity is upheld.

a) In compliance with CTRC standard operating procedures and University of Liverpool policies, no unauthorised users can gain access to clinical information systems both internally and externally. A log of authorised users will be kept with access details.

b) Destruction of data after proposed term of use - In compliance with CTRC standard operating procedures and University of Liverpool policies, no data will be kept longer than stated. CTRC destruction procedures will be applied.

c) Servers held in access controlled server rooms.

d) Servers backed up every night

e) Data collected using GCP compliant systems

### 5.5. Indemnity

The University of Liverpool holds indemnity and insurance cover with Marsh UK LTD, which apply to this study.

### 5.6. Sponsor

The University of Liverpool will be asked to act as the Sponsor for this study.

### 5.7. Audits

The study may be subject to inspection and audit by the University of Liverpool under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

## 6. End of the Study

The study will end when the enhanced surveillance system component has been operational for two consecutive winter seasons (November to April).

## 7. Archiving

Clinical Samples:

Consent will be obtained for storing clinical samples (stool and saliva) for further ethically approved research beyond this proposal. Samples will be archived and stored frozen at the Ronald Ross Building, Institute of Infection and Global Health, University of Liverpool, 8 West Derby Street, L69 7BE. Samples will be stored for 5 years after the end of the study. Key members of the study team will have access. Prof Miren Iturriza-Gomara will be the named custodian and Qibo Zhang is the IGH Human Tissue co-ordinator.

Data:

All raw and modified data will be stored locally using appropriate file formats. Only pseudonymised data will be retained; all personal identifiers will be removed. The research team will hold the database linking participant identifiers and study IDs on a password protected database at a secure location at the University of Liverpool. Study data will be held on password protected databases using a variety of formats including Access and SQL. For most data types, standard file formats will be used (e.g. text, Excel, Word, Access files) and data storage requirements will be manageable through centralized file servers. Some data types, however, will be associated with proprietary formats and will require significant storage requirements. Examples include microbiota sequencing. Raw data files will be processed locally and stored as standard data files to allow sharing as appropriate. Some data types, for example microbiota data, will be archived in data archives with appropriate procedures for data access and sharing, for example the EBI metagenomics database. The Centre for Genomic Research also assists in the archiving of data in central repositories, such as the European Nucleotide Archive in a timely and responsible manner, using established formats. Raw sequence data (Illumina MiSeq) will be made available to the EBI sequence read archive as soon as practicable after sequence data generation and analysis. Following publication, we will not place limits on access to either raw or processed sequence data.

The project will generate data that may have utility to address research questions beyond those outlined in the study proposal. The data repositories that are used have been mentioned above. If additional scientific benefits may be generated, anonymised data and clinical samples will be shared with other researchers. Any shared data will be of high quality and in a format which will enable effective use. Data of significant value to the community may be shared as soon as feasible, but a minimum may be made available to other researchers following publication. Data will be made available with as few restrictions as possible, while maintaining participant confidentiality. No patient identifiable data will be shared. Specific consent for data sharing will be sought as part of the informed consent process at study recruitment.

Research records and related material will be retained for a minimum of 10 years after the study has been completed in accordance with the MRC’s guidance on data and material storage. Paper records will be stored securely by the University of Liverpool Records Management Service.

## 8. Publication Policy

Study results will be presented and discussed at appropriate scientific meetings, and published in open access peer reviewed journals. Appropriate metadata will be published with the research data to enable other researchers to identify whether the data could be suitable for their own research. No identifiable personal data will be published; small counts of cells will be suppressed if it is possible to infer personal identifiable data by cross-referencing.

**Presentation at meetings (Oral and Poster)**

An up-to-date list of meetings where presentations have been made will be maintained.

**Interim results**

Interim results will be presented following discussion among the study lead investigators. Conference abstracts suggesting the presentation of interim results should be agreed by the study leaders prior to submission.

**Publication in Journals**

*Authorship*

All members of the study will be offered the opportunity to contribute to papers and authorship for each paper will be dependent upon contribution. The authors primarily responsible for the manuscript will be identified at an early stage.

*Acknowledgments*

The funders of this study will be appropriately acknowledged in any publication and presentation at meetings. All publications should acknowledge the contribution made by the wider study team.

**Spin-off Projects**

If a spin-off project to the Study is agreed among the study lead investigators, it is essential that the researchers of the study comply with the terms and conditions of collaboration and publication as above.

## 9. Study team

Principal Investigator:

* Prof Sarah O’Brien, Public Health epidemiologist, Director of NIHR HPRU in Gastrointestinal Infections, Institute of Infection and Global Health, University of Liverpool

Co-Investigators:

* Thomas Inns, PhD Student, Institute of Infection and Global Health, University of Liverpool
* Anna Pulawska-Czub, PhD Student, Institute of Infection and Global Health, University of Liverpool
* Prof Miren Iturriza Gomara, Virologist, Institute of Infection and Global Health, University of Liverpool
* Dr John Harris, Lecturer in Health Protection, University of Liverpool
* Dr Roberto Vivancos, Regional Epidemiologist, Consultant in Communicable Diseases, Field Epidemiology Services, Public Health England
* Dr Jon Read, Senior Lecturer in infectious disease epidemiology, Lancaster University
* Dr Nicholas Beeching, Clinical Lead, Tropical and Infectious Disease Unit, Royal Liverpool and Broadgreen University Hospitals Trust (RLUH), Honorary Consultant with PHE
* Dr David J Allen, Unit Head, Enteric Virus Unit, Public Health England
* Infectious disease research nurses (to be decided based on availability)

**Study steering group**

Members of the study team will form the basis of the study steering group. Each study site will have one place on the study steering group; this will be filled by a participant who volunteers. A lay member of the Health Protection Research Unit in Gastrointestinal Infections External Advisory Panel will also be asked to join the study steering group. The steering group will meet quarterly and discuss the operation and management of the study, along with the analysis of results and dissemination of findings.

## 10. Study resources

This study will be funded with a total of £79,345 from the NIHR Health Protection Research Unit in Gastrointestinal Infections. In addition to this funding, 1.5 WTE research nurses will be available to work on this study.

**Feasibility**

Data from Public Health England surveillance of gastrointestinal illness in care homes in Cheshire and Merseyside indicate that the median number of residents is 32 and the median number of staff is 35. Using this information, we can expect that there will be 67 participants per study site. We will aim to recruit four study sites prospectively. We therefore estimate that there will be 268 participants at sites enrolled prospectively.

The rate of UK-acquired IID, standardized to the age and sex distribution of the UK population, was 274 cases per 1000 person-years (88). Given that we estimate 268 participants will be followed up for approximately 2 year, this would be 536 person-years and we may therefore expect 147 episodes which will meet the case definition and require pathogen testing of a stool sample.

Although final costings for the Luminex pathogen testing are not currently available, the study funding will be sufficient for all material and service costs for sample testing outlined in this study protocol.

In recognition of the extra work that sample collection will add to staff time and to encourage sample collection, we will provide a £5 voucher for each stool sample that fits the study criteria. This voucher will be given to the person collecting the sample.

## 11. Project Timeline

Please see below for a Gantt chart showing an anticipated timeline for work associated with the study. The Gantt chart shows the work by year and month.



## 12. References

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## Appendix 1.1 – Care home background questionnaire

1) Name of care home: ………………………………………………………………………………………….

|  |  |  |
| --- | --- | --- |
|  |  |  |

2) Care home ID (Assigned by study team)

3) Care home address:…………………………………………………………………………………………….

4) Care home postcode: …………………………………………..

5) Name of Registered Manager:……………………………………………………………………………..

6) Name of main contact (if different):……………………………………………………………………..

7) Contact telephone number:………………………………………………………………………………….

8) Contact email address:…………………………………………...

9) Total resident capacity:………………………

10) Total number of staff:………………………… (including catering and bank staff)

11) Total number of qualified nursing staff:……………………… (including agency and bank staff)

Signature of Registered Manager Date of signature

…………………………………………………………………………………………. ……../……../…………

Signature of study team member Date of signature

…………………………………………………………………………………………. ……../……../…………

## Appendix 1.2 – Participant demographic information



**Participant demographic information questionnaire**

|  |  |  |
| --- | --- | --- |
|  |  |  |

1) Care home ID:

2) Name of person completing the report:……………………………………………………………..

3) Date of report: ……../………/…………. (dd/mm/yyyy)

**Details of the participant:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

4) Participant ID: (Assigned by study team)

5) Surname:…………………………………………. 6) Forename (s):……………………………………………………

7) Date of birth: ……../………/…………. (dd/mm/yyyy) 8) Gender: ………………..

9) Name and address of registered GP practice:………………………………………………………………………………..

………………………………………………………………………………….

………………………………………………………………………………….

………………………………………………………………………………….

10) Name of participant’s GP: ………………………………………………………………………………….

**If the participant is a resident:**

11) Date of arrival at the home: ……../………/…………. (dd/mm/yyyy)

12) Room number:…………………. 13) Which floor is the room on? ………………………….

*Questionnaire continues on the next page*

**If the participant is a member of staff:**

14) Date which you started working at the home: ……../………/…………. (dd/mm/yyyy)

15) Hours worked per week (average):………………….

16) Job title:…………………………………………………………………………………………………………………………

## Appendix 1.3 – Care home current capacity questionnaire

|  |  |  |
| --- | --- | --- |
|  |  |  |

1) Care home ID:

2) Name of person completing the report:……………………………………………………………..

3) Date of report: ……../………/…………. (dd/mm/yyyy)

**As of today, what is the…**

4) Total number of residents: …………………….

5) Total capacity for residents:……………………

6) Total number of staff:………………………… (including catering and bank staff)

7) Total number of qualified nursing staff:……………………… (including agency and bank staff)

## Appendix 1.4 – Individual case reports



**Individual case report**

|  |  |  |
| --- | --- | --- |
|  |  |  |

1) Care home ID:

2) Name of person completing the report:……………………………………………………………..

3) Date of report: ……../………/…………. (dd/mm/yyyy)

**Details of the person who is ill:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

4) Participant ID:

5) Date of first symptom: ……../………/…………. (dd/mm/yyyy)

6) Does the person have the following symptoms?

Diarrhoea Y / N

Vomiting Y / N

Nausea Y / N

Blood in stools Y / N

Abdominal pain Y / N

Fever Y / N

Headache Y / N

7) Has a stool specimen been taken? Y / N

8) Has the person been admitted to hospital? Y / N

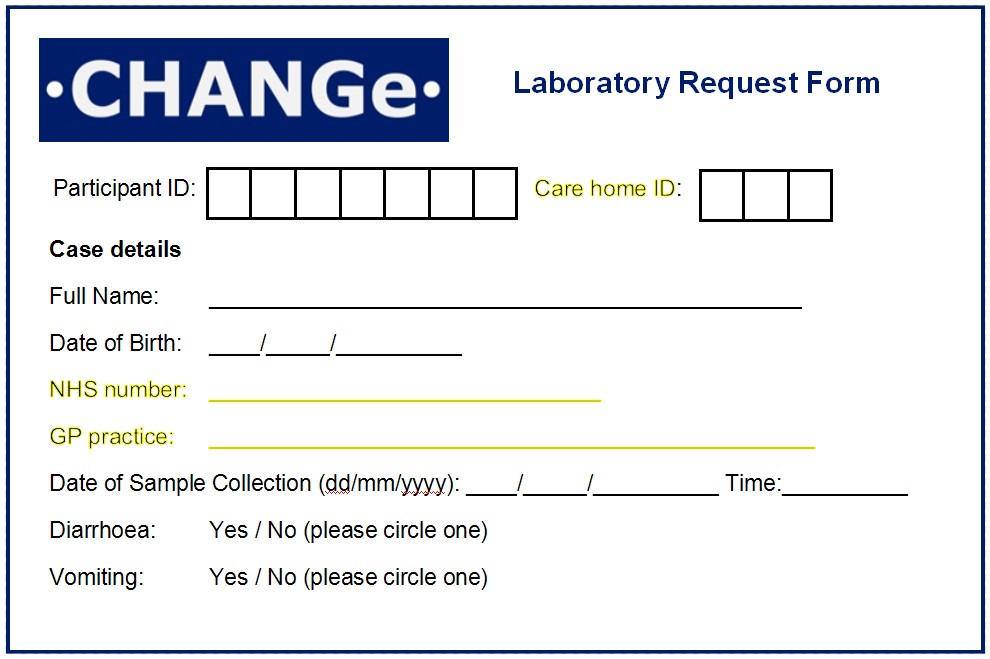
9) Is the person taking any antibiotic medication? Y / N

If yes, please list…………………………………………………………………………………………………………..

10) Is the person taking any statins? Y / N

(e.g. Lipitor, Lescol, Lipostat, Crestor, Zocor)

## Appendix 1.5. – Stool sample testing request form



## Appendix 1.6 – Transmission study data collection



**Transmission study data collection form**

|  |  |  |
| --- | --- | --- |
|  |  |  |

1) Care home ID:

2) Name of person completing the form:……………………………………………………………..

3) Date of completion: ……../………/…………. (dd/mm/yyyy)

**Details of the participant:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

4) Participant ID:

5) Number of mote assigned:…………………………………………………………….

6) Time of mote handover:…………………………………….. (24 hour clock)

7) Participant group: (circle one)

Resident Staff member Visitor

8) If staff, type of role: (circle one)

Administrative Care Nursing Other

9) Time of mote return:…………………………………….. (24 hour clock)

## Appendix 1.7 – Norovirus exposure questionnaire



**Norovirus exposure questionnaire**

|  |  |  |
| --- | --- | --- |
|  |  |  |

1) Care home ID:

2) Name of person completing the report:……………………………………………………………..

3) Date of report: ……../………/…………. (dd/mm/yyyy)

**Details of the participant:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |

4) Participant ID:

5) Did this person meet the case definition? Y / N

6) If yes, first date of symptoms:……./………/……………. (dd/mm/yyyy)

**Exposures**

For **all** participants, please answer the following questions based on **the outbreak period**.

7) Did the person leave their room at any point? Y / N

8) If yes, did the person visit the following areas?

Communal area A Y / N

Communal area B Y / N

Dining area A Y / N

Dining area B Y / N

Garden area Y / N

9) Did the person eat any of the following foods:

Day -1: Breakfast food Y / N

Day -1: Lunch food A Y / N

Day -1 Lunch food B Y / N

Day -1: Dinner choice A Y / N

Day -1: Dinner choice B Y / N

Day -2: Breakfast food Y / N

Day -2: Lunch food A Y / N

Day -2 Lunch food B Y / N

Day -2: Dinner choice A Y / N

Day -2: Dinner choice B Y / N

Day -3: Breakfast food Y / N

Day -3: Lunch food A Y / N

Day -3 Lunch food B Y / N

Day -3: Dinner choice A Y / N

Day -3: Dinner choice B Y / N

## Appendix 1.8 – Questionnaire to assess quantitative impact of outbreaks

|  |  |  |
| --- | --- | --- |
|  |  |  |

1) Care home ID:

2) Name of person completing the report:……………………………………………………………..

3) Date of report: ……../………/…………. (dd/mm/yyyy)

For completion by study team member:

4) Outbreak start date: ……../………/…………. (dd/mm/yyyy)

5) Outbreak end date: ……../………/…………. (dd/mm/yyyy)

6) Non-outbreak start date: ……../………/…………. (dd/mm/yyyy)

7) Non-outbreak end date: ……../………/…………. (dd/mm/yyyy)

For completion by staff at study site

At the outbreak start date:

8) Number of resident cases: ………………

9) Number of residents: ………………

10) Number of staff cases: ………………

11) Total number of staff: ……………… (including catering and bank staff)

12) Total number of qualified nursing staff:………… (including agency and bank staff)

13) Number of staff days off: ………………

14) Cost of additional staff (£): ………………

15) Cost of additional cleaning (£): ……………..

16) Number of residents isolated: ……………..

17) Total number of isolated resident days:……………….

18) Number of cases transferred to hospital:………………….

19) Number of resident admissions delayed:………………….

At the non-outbreak start date:

20) Number of residents: ………………

21) Total number of staff: ……………… (including catering and bank staff)

22) Total number of qualified nursing staff:………… (including agency and bank staff)

23) Number of staff days off: ………………

## Appendix 1.9 – Full list of data items to be collected

3.3.1. Enhanced surveillance system

Background study site information (Appendix 1.1)

Data item collected // Format // Frequency

Study site name string once

Study site address string once

Study site postcode string once

Name of Registered Manager string once

Study site key contact person string once

Study site contact telephone number string once

Study site contact email address string once

Study site resident capacity integer once

Study site total staff number integer once

Study site number qualified nursing staff integer once

Participant demographic information (Appendix 1.2)

Data item collected // Format // Frequency

Care home ID string once

Name of person completing the report string once

Date of report dd/mm/yyyy once

Details of the participant

Surname string once

Forename string once

Date of birth dd/mm/yyyy once

Gender integer once

Name and address of GP practice string once

Name of participant’s GP string once

If the participant is a resident

Date of arrival at the home dd/mm/yyyy once

Room number string once

Which floor is the room on string once

If the participant is a member of staff:

Date which you started working at the home dd/mm/yyyy once

Hours worked per week (average) integer once

Job title string once

Study site current capacity information (Appendix 1.3)

Data item collected // Format // Frequency

Care home ID string monthly

Name of person completing the report string monthly

Date of report dd/mm/yyyy monthly

Current number of residents integer monthly

Current study site capacity integer monthly

Current total staff number integer monthly

Current number of qualified nursing staff integer monthly

Individual case reports (Appendix 1.4)

Data item collected // Format // Frequency

Care home ID string once

Name of person completing the report string once

Date of report dd/mm/yyyy once

Participant ID string once

Case first symptom date dd/mm/yyyy once

Case diarrhoea integer once

Case vomiting integer once

Case nausea integer once

Case blood in stools integer once

Case abdominal pain integer once

Case fever integer once

Case headaches integer once

Has a stool sample been taken integer once

Case admitted to hospital integer once

Case taking antibiotics integer once

List of antibiotics string once

Case taking statins integer once

3.3.2. Pathogen testing (Appendix 1.5)

Data item collected // Format // Frequency

Sample case surname string once

Sample case forename string once

Sample case date of birth dd/mm/yyyy once

Sample participant ID string once

Sample care home ID string once

Sample case NHS number integer once

Sample case GP practice string once

Sample date dd/mm/yyyy once

Sample pathogen found string once

Sample norovirus typing result string once

3.3.3. Individual risk factors for norovirus infection

Data item collected // Format // Frequency

Participant ID string once

Stool sample date dd/mm/yyyy once

Stool sample case status integer once

Stool sample case/control identifier integer once

Sample qRT-PCR result string once

Sample qRT-PCR interpretation string once

Sample EIA assay result string once

Sample EIA result interpretation string once

Saliva sample date dd/mm/yyyy once

Saliva sample surname string once

Saliva sample forename string once

Saliva sample date of birth dd/mm/yyyy once

Saliva sample case status integer once

Saliva sample participant identifier integer once

Saliva sample blood group result string once

3.3.5. Transmission dynamics study data collection (Appendix 1.6)

Data item collected // Format // Frequency

Care home ID string once

Name of person completing the report string once

Date of report dd/mm/yyyy once

Participant ID string once

Number of mote assigned integer once

Time of mote handover hh:mm once

Participant group integer once

Participant staff role integer once

Time of mote return hh:mm once

Mote-generated contact matrix (ob) matrix repeated

Mote-generated contact matrix (non-ob) matrix repeated

3.3.5. Risk factors during outbreaks (Appendix 1.7)

Data item collected // Format // Frequency

Care home ID string once

Person completing report string once

Date of report dd/mm/yyyy once

Participant ID string once

Defined as case integer once

First date of symptoms dd/mm/yyyy once

Person left room integer once

Communal area A integer once

Communal area B integer once

Dining area A integer once

Dining area B integer once

Garden area integer once

Day -1: Breakfast food integer once

Day -1: Lunch food A integer once

Day -1 Lunch food B integer once

Day -1: Dinner choice A integer once

Day -1: Dinner choice B integer once

Day -2: Breakfast food integer once

Day -2: Lunch food A integer once

Day -2 Lunch food B integer once

Day -2: Dinner choice A integer once

Day -2: Dinner choice B integer once

Day -3: Breakfast food integer once

Day -3: Lunch food A integer once

Day -3 Lunch food B integer once

Day -3: Dinner choice A integer once

Day -3: Dinner choice B integer once

3.3.7. Questionnaire to assess quantitative impact of outbreaks (Appendix 1.8)

Data item collected // Format // Frequency

Care home ID string once

Person completing report string once

Date of report dd/mm/yyyy once

Outbreak start date dd/mm/yyyy once

Outbreak end date dd/mm/yyyy once

Non-outbreak start date dd/mm/yyyy once

Non-outbreak end date dd/mm/yyyy once

During outbreak

Number of resident cases integer once

Number of residents at outbreak start date integer once

Number of staff cases integer once

Total number of staff integer once

Total number of qualified nursing staff integer once

Number of staff days lost integer once

Cost of additional staff (£) integer multiple

Cost of additional cleaning (£) integer multiple

Number of residents isolated integer multiple

Total number of isolated resident-days integer multiple

Number of cases transferred to hospital integer multiple

Number of inward transfers delayed integer multiple

Non-outbreak

Number of residents at non-outbreak start date integer once

Total number of staff integer once

Total number of qualified nursing staff integer once

Number of staff days lost integer once

## Appendix 2.1 – Guidance for collecting stool specimens

**How to collect a stool sample for laboratory tests**

 **In your envelope you will find:**

* The sample pot (blue top), this has a small plastic spoon fitted to the underside of the lid
* A plastic bag
* Plastic gloves
* A stool sample collection device (Fe-Col®)
* A sample form

**Information to be provided with the sample:**

*Label on sample pot:*

Fill in details on the label on the sample pot (blue top), to include: participant’s full name and date of birth.

*Laboratory Request Form*

Fill in the details on the Laboratory Request Form

**Instructions about how to collect a mobile adult’s stool sample**

* Use a clean toilet which has been well flushed
* Wash your hands thoroughly, using soap and running water, then dry well**.**
* If you want to use the gloves provided, put them on.

Open the stool sample collection device and place the biodegradable paper loop over the toilet seat. Sit over the loop to pass stool, and when you have finished, collect a sample with the spoon provided in the blue screw cap tube.

Try to scoop enough of the stool from a soiled pad to fill the sample pot to the 5 ml marker. However, if this is not possible, obtain as much of the stool as you can.

Place blue topwith spoon over the collection tube and screw it tightly.

Tear the paper loop and drop it into the toilet bowl. Flush the toilet normally.



**Instructions about how to collect an immobile adult’s stool sample.**

Use the plastic spoon fitted to the sample pot lid to scoop enough of the stool from a soiled pad to fill the sample pot to the 5 ml marker. However, if this is not possible, obtain as much of the stool as you can**.**

**Please note:**

Try not to spill the stool on the outside of the sample pot. If this happens please clean the outside of the sample pot with soap and warm water, wash your hands thoroughly, then dry the sample pot and your hands well.

**When you have finished collecting the sample**

Put anything you have used to collect the sample, eg, plastic gloves, soiled pad,

in a plastic bag, tie up the bag and put it in the bin.

Wash your hands thoroughly, using soap and running water, then dry well**.**

Place the sample pot in the plastic bag.

Keep the package in a cool place (but not your fridge)

**It is important that stool samples reach the laboratory as “fresh” as possible (within 12 hr of collection) as longer storage time can affect the test results.**

**In order to arrange collection please call the following number: XXXXXXXXXXX**

***Thank you for your co-operation***

## Appendix 2.2 – Guidance for collecting saliva specimens

**Saliva collection method with SalivaBio Oral Swab (SOS) Salimetrics®**

**METHODOLOGY AND PROCEDURES**

1. **Collection of saliva samples**
   1. Rinse mouth with water to remove food residue before sample collection
   2. Peel back protective package and remove the swab
   3. Place the swab between cheek and gums and rub it against gums for 1 minute in order to obtain cells for DNA isolation
   4. Relocate the swab underneath the tongue and collect saliva for 1 minute
   5. Remove cap from the storage tube
   6. Remove swab from mouth and immediately place the swab to insert of the swab storage tube (“basket”)
   7. Recap storage tube tightly
   8. Label the exterior storage tube with the participant ID

**TIMING OF SAMPLE DELIVERY**

Samples will be delivered within 6 hours of being obtained.

a) Swab for self-sampling



b) Swab for aided sampling (long enough to allow one end of the swab to be held whilst in the participant’s mouth, eliminating any choking hazard.





## Appendix 3.1 - Study Consent Form

Study name: Study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside

Name of researcher: Mr Thomas Inns / Prof Sarah O’Brien

Please **place your initials next to the statements below that you agree with**: Initial

|  |  |  |  |
| --- | --- | --- | --- |
| 1 | I have read/been read the information sheet for the study. I have had the chance to ask questions and am happy with the answers. |  |  |
| 2 | I agree to be asked about my health for this study. |  |  |
| 3 | I agree that stool samples can be taken from me and stored for the purpose of this study. |  |  |
| 4 | I agree that saliva samples can be taken from me and stored for the purpose of this study. |  |  |
| 5 | I agree that my samples can be stored and used for future ethically approved research studies. |  |  |
| 6 | I agree that my proximity to other people may be recorded using a low-power radio-frequency device for the purpose of this study |  |  |
| 7 | I agree that approved study staff will have access to my medical records |  |  |
| 8 | I understand that only approved study staff will have access to information that could identify me. |  |  |
| 9 | I understand that information collected in this study that cannot be used to identify me may be shared with other researchers conducting studies to benefit others. |  |  |
| 10 | I understand that taking part in this study is voluntary and that I can withdraw at any time, without giving a reason and without this affecting my medical care. |  |  |
| 11 | I understand that if I lose the capacity to consent during the study, I will be withdrawn and any identifiable data or samples will be retained and used in the study |  |  |

Print Name of participant: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature of participant: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of person obtaining consent:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature of study staff \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date\_\_\_\_\_\_\_\_\_\_\_\_\_

*Consent form version 1.1 30/08/2016*

## Appendix 3.2 – Study information for visitors



**Study Information for visitors**

Local Principal Investigator: Thomas Inns

Chief Investigator: Prof Sarah O’Brien

Study name: CHANGe – a study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside

**Why we need your help**

We are trying to reduce the number of people that fall ill with diarrhoea and vomiting. In the UK, the most common cause of diarrhoea and vomiting in adults is an infection called norovirus.

The purpose of this research is to understand how many people in care homes get diarrhoea and vomiting, find out what causes it and how it is spread.

**Why me?**

You have been asked to take part in the study because you are visiting one of the study sites

**What sort of study is this?**

This is an observational research study that is taking place in care homes in Liverpool and Sefton.

**What will I be asked to do?**

If you agree to take part in the study, we will do the following:

1. Ask you to help us complete a short questionnaire which will collect demographic information about you.

2. We will ask you to keep a small low-power radio frequency device (“mote”) close-by while you are at the care home; to work out how diseases that cause diarrhoea and vomiting are spread in care homes.

**What is a “mote”?**

A mote is a small (2.5cm x 7.5 cm x 2 cm) electronic device powered by two AA batteries. A mote sends out a weak radio signal, similar to a cordless phone, every 20 seconds, and records the signals of any other motes.

**Are there any risks to taking part in the study?**

There are no risks to taking part in the study.

**What are the benefits of taking part in the study?**

There is no direct benefit to participants. You will be helping us to improve our knowledge of how diseases that cause diarrhoea and vomiting spread in care homes and how to avoid it.

**What happens if I decide to take part in the study?**

All you have to do is complete the consent form, which tells us that you are happy to take part in the study.

**What happens if I leave the study?**

You can stop taking part in the study at any time. You do not need to explain why. We will ask your permission to use any information or results we have obtained up until the point you stop taking part. If you do not give us permission to do this, we will remove all files and data relating to you.

**Who has checked the study?**

This study will be checked by the NRES ??? Research Ethics Committee of the National Health Service.

**Will my information be secure?**

Yes. We will adhere to the Data Protection Act (1998), which tells us how to keep your data secure.

The information that we collect will be stored on a secure network, and will only be accessed by authorised members of the study team using special passwords. We will not give your details to anyone else. Your name or any information that might be used to identify you will be kept anonymous.

**What will happen at the end of the study?**

The results of the study will be published in scientific journals with open access and presented at various scientific conferences. We will not use your name or any information that might be used to identify you.

**Who is organising and paying for this study?**

The University of Liverpool is organising this study. This study is funded by the National Institute for Health Research: Health Protection Research Unit in Gastrointestinal Infections.

**Where can I get further information?**

If you have any questions about taking part in the study, please contact: Thomas Inns by email at thomas.inns@liverpool.ac.uk or by telephone on 0151 794 9871.

If you are unhappy about any aspect of this study and want to make a complaint you can do this through the NHS Complaints Procedure.

*Study information for visitors v1.1 30/08/2016*



## Appendix 3.3 – Study consent form for visitors

Study name: CHANGe -a study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside

Name of researcher: Mr Thomas Inns / Prof Sarah O’Brien

Please **place your initials next to the statements below that you agree with**: Initial

|  |  |  |  |
| --- | --- | --- | --- |
| 1 | I have read/been read the information sheet for the study. I have had the chance to ask questions and am happy with the answers. |  |  |
| 2 | I agree that my proximity to other people may be recorded using a low-power radio-frequency device for the purpose of this study |  |  |
| 3 | I understand that only approved study staff will have access to information that could identify me. |  |  |
| 4 | I understand that information collected in this study that cannot be used to identify me may be shared with other researchers conducting studies to benefit others. |  |  |
| 5 | I understand that taking part in this study is voluntary and that I can withdraw at any time, without giving a reason and without this affecting my medical care. |  |  |

|  |  |  |
| --- | --- | --- |
| **I agree to take part in the study** |  |  |

Name of participant: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature of participant: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Print name of participant: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of study staff obtaining consent:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature of study staff \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date\_\_\_\_\_\_\_\_\_\_\_\_\_

*Consent form for visitors version 1.0 03/06/2016*

## Appendix 3.4 – Study participant information leaflet (resident)

Please see attached document “20160830\_participant\_info\_leaflet\_resident.pdf”

## Appendix 3.5 – Study participant information leaflet (staff)

Please see attached document “20160830\_participant\_info\_leaflet\_staff.pdf”

## Appendix 3.6 – Study participant information leaflet (nominated person)

Please see attached document “20160830\_participant\_info\_leaflet\_nominated\_person.pdf”

## Appendix 3.7 – Study participant letter of invitation



Local Principal Investigator: Thomas Inns

Chief Investigator: Prof. Sarah O’Brien

Study name: CHANGe – a study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside

Dear Sir/Madam,

We would like to invite you to take part in this research study. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what will happen if you agree to take part.

We are trying to reduce the number of people that fall ill with diarrhoea and vomiting. In the UK, the most common cause of diarrhoea and vomiting in adults is an infection called norovirus.

The purpose of this research is to understand how many people in care homes get diarrhoea and vomiting, find out what causes it and how it is spread.

Please take time to read this information sheet carefully and to ask any questions you might have. It is important to understand that you do not have to accept this invitation and should only agree to take part if you want to.

Yours sincerely,

SARAH O’BRIEN SIGNATURE

Prof Sarah O'Brien MB BS, FRCP, FFPHM, DTM&H

Professor of Infection Epidemiology and Zoonoses

Epidemiology and Population Health

University of Liverpool

*Study letter of participant invitation version 1.0 24/02/2016*

## Appendix 3.8 – Letter to GP following participant consent



|  |  |
| --- | --- |
| Study participant number: |  |

Chief Investigator: Prof Sarah O’Brien

Dear Dr ......................................

On behalf of the study team, we would like to inform you that \_\_\_\_\_\_\_\_\_\_\_\_ registered at your practice, has consented to take part in the CHANGe study; this is a study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside.

A copy of the participant information leaflet is enclosed. The study has been sponsored by the University of Liverpool. Appropriate NHS ethical approval has also been obtained.

This is an observational study, participants will be asked to submit a stool sample and receive enhanced testing if they experience acute gastroenteritis. Participants will also be asked to provide a saliva sample to test for blood group. Participants may be asked to provide a stool sample to test for norovirus on occasions when they have not experienced acute gastroenteritis and they may be asked to anonymously record their contact with other participants using low-power radio frequency devices.

If you have any further questions about the study please contact Thomas Inns by email at thomas.inns@liverpool.ac.uk or by telephone on 0151 794 9871.

With best wishes,

SARAH O’BRIEN SIGNATURE

Prof Sarah O'Brien MB BS, FRCP, FFPHM, DTM&H

Professor of Infection Epidemiology and Zoonoses

Epidemiology and Population Health

University of Liverpool

*Letter to General Practitioner version 1.0 03/06/2016*



## Appendix 3.9 - Study Assent Form

Study name: Study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside

Name of researcher: Mr Thomas Inns / Prof Sarah O’Brien

Please **place your initials next to the statements below that you agree with**: Initial

|  |  |  |  |
| --- | --- | --- | --- |
| 1 | I have read/been read the information sheet for the study. I have had the chance to ask questions and am happy with the answers. |  |  |
| 2 | I agree that the participant can be asked about their health for this study. |  |  |
| 3 | I agree that stool samples can be taken from the participant and stored for the purpose of this study. |  |  |
| 4 | I agree that saliva samples can be taken from the participant and stored for the purpose of this study. |  |  |
| 5 | I agree that samples taken from the participant can be stored and used for future ethically approved research studies. |  |  |
| 6 | I agree that the proximity of the participant to other people may be recorded using a low-power radio-frequency device for the purpose of this study |  |  |
| 7 | I agree that approved study staff will have access to the participant’s medical records |  |  |
| 8 | I understand that only approved study staff will have access to information that could identify the participant. |  |  |
| 9 | I understand that information collected in this study that cannot be used to identify the participant may be shared with other researchers conducting studies to benefit others. |  |  |
| 10 | I understand that taking part in this study is voluntary and that the participant can withdraw at any time, without giving a reason and without this affecting that participant’s medical care. |  |  |

Name of participant: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of the person assenting on behalf of the participant: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature of person assenting: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*Office use only*

Name of person obtaining assent:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature of study staff \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date\_\_\_\_\_\_\_\_\_\_\_\_\_

*Study assent form version 1.2 23/11/2017*

## Appendix 4.0 – Nominated person letter of information



Local Principal Investigator: Thomas Inns

Chief Investigator: Prof. Sarah O’Brien

Study name: CHANGe – a study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside

Dear Sir/Madam,

We have contacted you as we are conducting a research study. The purpose of this research is to understand how many people in care homes get diarrhoea and vomiting, find out what causes it and how it is spread.

We are trying to reduce the number of people that fall ill with diarrhoea and vomiting. In the UK, the most common cause of diarrhoea and vomiting in adults is an infection called norovirus.

You have been identified by (insert name of care home) as the nominated person for someone that we would like to participate in the study. We would like to consult you in accordance with the Mental Capacity Act 2005. We would like to find out what this person’s wishes would be about taking part in the project and your advice as to whether the person should take part.

Before you decide whether you agree for this person to take part in the study, it is important for you to understand why the research is being done and what will happen if you agree that they should take part.

Please take time to read this information sheet carefully and to ask any questions you might have. It is important to understand that you do not have to accept this invitation on their behalf. If you believe that the person would want to take part in the study, please initial and sign the enclosed assent form.

Yours sincerely,

SARAH O’BRIEN SIGNATURE

Prof Sarah O'Brien MB BS, FRCP, FFPHM, DTM&H

Professor of Infection Epidemiology and Zoonoses

Epidemiology and Population Health

University of Liverpool

*Nominated person letter of information version 1.1 30/08/2016*