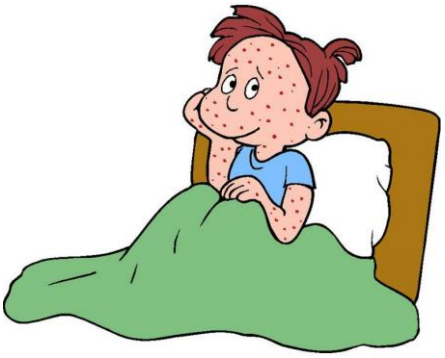

Study Protocol

Study Title:	Quality of Life Effects of Chickenpox on Hospitalised Children and their Families.
Acronym:	QoL-PoX – H
Ethics ref:	18/ES/0040
Version and Date:	Version 1.5 (27/11/2019)
Chief Investigator:	Dr Robin Marlow. Robin.Marlow@bristol.ac.uk University of Bristol (UoB), School of Clinical Sciences Level 6, UHB Education Centre, Upper Maudlin Street, Bristol, BS2 8AE, UK
Investigators:	Dr Marion Roderick, Paediatric Infectious Diseases Consultant Hannah Christensen, Lecturer in Infectious Disease Mathematical Modelling Professor Adam Finn, Professor of Paediatrics, University of Bristol
Sponsor:	The University of Bristol.

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s)	Details of Changes made
1	1.1		RM	External peer reviewer comments addressed
	1.2	18/02/18	RM	Based on further review sample size increased. Surveillance aspect moved into separate protocol.
	1.3	20/3/18	RM	Updated to reflect multisite nature of study
	1.4	12/06/19	RM	Minor clarifications and corrections
	1.5	27/11/19	RM	Adjust to allow inclusion of children on outpatient parenteral antibiotics and extension of end-date Link to University insurance certificate

Signed by Chief Investigator:

Dr Robin Marlow

Signed by Sponsor

2. SYNOPSIS

Study Title	Quality of Life Effects of Chickenpox on Hospitalised Children and their Families.
Internal ref. no.	QoL-PoX - hospital
Study Design	Observational Cohort Study
Study Participants	Children aged 0-16 years and their carers
Planned Sample Size	100 (but to allow possible over recruitment to 200)
Follow-up duration	Up to 6 months after hospital discharge.
Planned Study Period	1st March-2018 1st Nov 2020 (30m recruitment+6m follow up)
Primary Objectives	To assess the impact of varicella disease on quality of life,
Secondary Objectives	To assess the impact of varicella disease on healthcare use, financial and health impact on family unit
Primary Outcome Measures	- QALY loss of patients and carers
Secondary Endpoints	- Wider financial and health impact on family members of affected patients
Intervention (s)	none

3. Relevant Study Documents

- Protocol (this document)
- Consent form
- Parent Information Sheet
- Child Information Sheet
- Daily Diary Inpatient (parental proxy + young person version)
- Weekly Diary for home (parental proxy + young person version)

4. INTRODUCTION

4.1. Rationale for study and study design

4.1.1. Epidemiology and burden of disease

Varicella Zoster (VZ) or chickenpox is a ubiquitous disease of childhood. Almost all children will catch it during the first five years of life[1]. It is spread through respiratory secretions or contact with vesicle fluid. After exposure the disease has a long asymptomatic incubation period of 10-21 days[2]. Children first become infectious during a two day generalised coryzal period before the development of the characteristic exanthema. This usually lasts for around five days before all spots are crusted and the child is no longer

infectious. Most children will have a mild course with the only inconvenience being an unpleasant itchy rash and time excluded from childcare. However some will go on to develop secondary complications, the most common being a bacterial infection of the lesions but with other serious complications such as stroke, encephalitis or pneumonitis occurring more rarely.[3] The relative proportions of children with these complications are poorly understood in the UK and will not be adequately captured by current routine surveillance.

4.1.2. Baseline for measuring rates of disease seeing hospital care

As chickenpox is not a notifiable disease, most of our knowledge of the epidemiology comes from routinely collected data on cases reported in the UK is available from the Royal College of General Practitioners Research and Surveillance Centre by sentinel GP practices in England and Wales. Admissions directly attributed to varicella may be identified through Hospital Episode statistics. These routinely collected datasets are likely to accurately capture cases of moderate varicella (the mildest cases will not seek any medical advice) but for secondary cases of e.g. cellulitis or childhood stroke the causal link with varicella may not be made clinically thus recorded or coded. The best data on complication rates in the UK is from a 2002 BPSU surveillance study.[4] However this used a very restrictive criteria for inclusion of severe cases so only identified a case incidence of 0.82/100,000 person years. In comparison a prospective surveillance study from Belgium found 29.5/100,000 person years of which 19/100,000 were complicated.[5]

4.1.1. Recent potential changes in UK epidemiology

There is an ongoing unexplained rise in the rates of invasive Group A streptococcal (iGAS) bacterial infections.[6] Evidence suggests that chickenpox is the most common risk factor for iGAS disease in children.[7] There is also evidence that the age distribution of children with VZV is shifting to affect increasingly younger children – the cause is not known but this is possibly due to rising rates of childcare facilitating increased mixing at a younger age.[8]

4.1.2. Impact on Health Related Quality of Life

The only study quantifying the health related quality of life (HRQoL) lost due to varicella in UK children used a convenience sample of forty two children attending primary care for other reasons whose mothers were asked to recall their child's quality of life at the time they had had chickenpox.[9] This suggested that the QALY loss due to VZV was 4 per 1000 patient cases. However the impact on carer HRQoL or social costs such as time from work / healthcare were not assessed. A similar retrospective method was used in Belgium finding a QALY loss of 4 per 1000 for children not seeking medical care but 10 per 1000 for those who had been ill enough to visit their General Practitioner.[10]

The HRQoL loss of patients hospitalised with VZV has not been assessed in the UK. In our study we will also be assessing carer HRQoL which although recommended by NICE to be included in economic analyses[11] is often overlooked and in previous studies we have found to be a significant additional burden of disease.[12] Of particular interest in children hospitalised with VZV is the persistence of long term sequelae. At discharge

from hospital children are unlikely to be back to a normal health state so we plan to follow them with additional diaries weekly for one month then a final follow up at six months.

4.1.3. Potential of Vaccination to prevent disease

Safe and effective vaccines exist against varicella. These have been in use in America since 1995[13] and Australia since 2005[14] with drastic reduction in rates of disease.[15] The question of UK vaccination has been debated for over a decade.[16] However the introduction to the UK has been stalled due to concerns of the potential for a rise in the rates of shingles in adults.[17] Whilst this has not been proven in practice in other countries[15,18] it currently still dominates the cost utility analysis for the UK models. The JCVI plan to review the evidence for the introduction of varicella vaccination in the UK and have highlighted this area in particular as of need for further research and data.

5. OBJECTIVES

5.1. Primary objectives

Identify a cohort of children in hospital with acute or recent chickenpox (within 21 days or within a year for cases of childhood stroke)[19,20] and follow them and their families during their illness to determine the impact on quality of life.

5.2. Secondary objectives

Determine the impact of varicella on healthcare use, financial and health impact on family unit

6. STUDY DESIGN

6.1. Summary of Study Design

This is a prospective observational cohort study with no active interventions nested within a routine surveillance programme.

6.2. Primary and Secondary Outcome Measures

6.2.1. Primary outcome measures

The primary outcome of the study is to calculate the loss of Quality Adjusted Life Years (QALYs) and financial cost attributable in the families of children with acute VZV infection. This will be measured by standard quality of life tools (EQ5D-5L[21] and CHU9[22] in children) and EQ5D-5L in adults.

6.2.2. Secondary outcome measures

We will collect data on disease severity using a previously validated assessment of symptoms tool[23] demographics, healthcare use, illness within the family unit and missed work / education days. We will

estimate the financial and societal costs for families through a daily diary inquiring about medication use, additional childcare costs and days of work missed.

6.3. Study Participants

6.3.1. Overall Description of Study Participants

As part of routine surveillance and our usual infection control procedures, parents of all children attending hospital are be asked about chickenpox or exposure within the last 21 days. [5] If they are admitted with 'stroke', then this time period will be varicella within the last 12 months.[19,20] As surveillance of severe complications, routine data will be recorded: nature of complication, length of stay, antibiotic and other drug use, imaging and pathology laboratory use. Patients identified within this surveillance group will be consented for inclusion into the QALY study.

6.3.2. Inclusion Criteria

- Male or Female, attending hospitalaged less than 16 years old.
- Currently have chickenpox or have had it during the last 21 days (12m for stroke).
- Informed consent obtained from the parent(s) with assent in children >6 years.

6.3.3. Exclusion Criteria

Only those for whom admission is felt to be clinically unrelated to recent varicella (e.g. injuries / new malignant diagnosis) should be excluded from the study.

6.3.4. Screening Data

We would also like sites to inform us if they become aware of any children who die as a result of VZV during the study period. We feel it would be unequivocally unethical to attempt to directly recruit these families, however with anonymous information on the number of cases (if any) and the age at which it occurred would allow use to incorporate this important data into the final analysis . This data will be routinely gathered as part of the case screening for the study.

6.4. Study Procedures

6.4.1. Patient identification

Study teams will carry out daily review of the hospital census to prospectively identify potential patients with chickenpox or a secondary complication. These will include but not limited to patients with skin infections, haemorrhagic vesicular rash, disseminated purpura, staphylococcal scalded skin syndrome, cellulitis, abscess, pneumonia, osteomyelitis, septic arthritis, myositis, adenitis, fasciitis, hepatitis, severe anorexia/dehydration, eye involvement, neurological issues, haematological disturbances or Reye's syndrome.[5] Any patient identified though this method will be invited to join this Quality of Life study.

Treating clinician will be asked to categorise cases into confirmed / likely / possible due to VZ and severity as Mild / Mod / Severe.

6.4.2. Informed Consent

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

Prior to enrolment and any study procedure, children's eligibility will be checked, and informed consent will be obtained. The parents or carers of participants must personally sign and date the informed consent form before any study specific procedures are performed and children over the age of six will be asked for assent. Written and verbal versions of the participant information and informed consent will be presented to the parents or carers detailing the exact nature of the study, the implications and constraints of the protocol. It will be clearly stated that they are free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

6.4.3. Study HRQoL Tool

Once consent is given, study personnel will provide a brief demographic questionnaire to the parent or guardian which will also ask them to score their child's HRQoL at the time of consent as well as retrospectively score their child's HRQoL prior to becoming illand if they are already recovering their HRQoL on the worst day of the illness. Parents will be given a brief demonstration and instructions of our diary system and asked to complete this daily (or alternate days) whilst in hospital (or receiving outpatient parenteral antibiotics / OPAT as part of hospital level care at home), weekly once discharged from hospital for one month and then monthly until their child's symptoms have completely resolved with a final contact again at six months.(figure 1) The diary will consist of illness severity questions and HRQoL questionnaires for the child and their parents taking less than 5 minutes to complete. Children over the age of 7 years will be able to fill out their own quality of life questionnaires themselves.

Parents will be offered reminder contact for the diary entries by phone / SMS / email, with the option of completing questions over the phone or internet.

We anticipate that for the families of children with severe disease as a result of varicella, engagement with the study aims will be high and with good communication and weekly reminders there should be limited dropout.

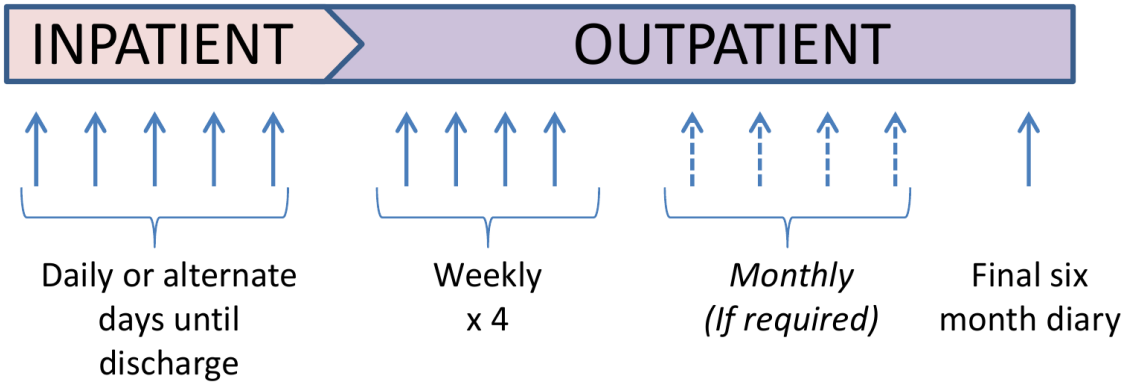

Figure 1: Timing of diary entries.(*INPATIENT includes receiving outpatient parenteral antibiotics / OPAT as part of hospital level care at home)

6.5. Definition of End of Study

The study is planned to recruit for up to 12 months and end of study will be the date of last diary entry of the last participant (up to 6 months after the last participant discharged from hospital).

7. DETAILS OF SAFETY REPORTING PROCESSES

As a prospective cohort study with no active interventions it will not result in adverse events. Parents should follow normal NHS clinical routes if they become unwell but will have contact details for the PI in case of study specific queries . The study is sponsored by the University of Bristol. The University has Public Liability insurance to cover the liability of the University to research participants.

http://www.bristol.ac.uk/media-library/sites/secretary/documents/insurance/employersandpublicliabilityletter.pdf.pdf

8. ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Methods & Sample size calculation

8.1.1. Primary objectives

We aim to recruit at least 100 families of children with chickenpox in hospital into the HRQoL surveillance arm but would ideally like to recruit 200. This will allow us to adequately quantify the differences in quality of life between ill and healthy states for different secondary complications and different ages. The previous historical recall studies[9],[10] do not describe the distribution of their HRQoL in enough detail to use in a power calculation.[24] Using the EQ5D reference healthy data[25] would suggest a sample size of 100 children would give 90% power to detect a 6% difference in quality of life (p=0.05). However as we would like to perform sub-group analysis for different types of secondary complication this will depend on the number in each group – with a minimum of 25. (personal communication Professor Nick Andrews Public Health England), ideally a sample size of 200 will increase the likelihood of capturing enough of each complication type to be able to analyse them separately.

8.1.2. Secondary objectives

These are descriptive analyses so have no formal power calculation. Incidence of complications will be calculated using the paediatric population for the hospital's referral area as a denominator taken from the Office for National Statistics population census.

8.2. Methods

Quality adjusted life year loss for children and their parents will be calculated as the reduction in HRQoL from baseline (as reported retrospectively prior to illness) for the time period between development of clinical signs and return to what the parents assess is normal health for their child. A sensitivity analysis will be carried out using baseline "healthy" cohort being assessed in a separate study.

9. SAMPLE PROCESSING / ANALYSIS / STORAGE

No samples will be collected as part of this study.

10. DATA HANDLING AND RECORD KEEPING

10.1. Patient Identification

Apart from the consent form, all study forms or questionnaires will be pseudo anonymised by the use a linked-study ID. This linkage will be broken as soon as data analysis is complete.

10.2. Data collection, recording and storage

All diary data will be non-personally identifiable using only a family study-ID to link back to the personal details stored on the consent form.

All documents will be stored securely and will only be accessible to trial staff and authorised personnel. Data will be collected and retained in accordance with the Data Protection Act 1998. Linkage details between study specific number and any clinical information will be stored on a separately held encrypted database. The study team will be responsible for data collection, recording and quality control. Study documents (paper and electronic) will be retained in a secure location during and after the study has finished. All source documents will be retained for a period of five years following the end of the study.

10.3. Monitoring and audit

The study will be monitored and audited in accordance with the University of Bristol policy. All study related documents will be made available on request for monitoring and audit by the University and the relevant Research Ethics Committee.

11. ETHICS

11.1. Study Conduct and Approvals

As research involving NHS participants the study will only be performed subject to NHS Research Ethics Committee (REC) and Health Research Agency (HRA) approval.

This study will recruit children who are not old enough to give consent. Informed consent will be obtained from the parent/legal guardian of each participant

The study will be conducted in accordance with:

- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines.
- UK Policy Framework for Health and Social Care Research
- The principles of the Declaration of Helsinki.

12. REPORTING AND DISSEMINATION OF RESULTS

It is anticipated that this research will lead to publications in a journals covering the areas of paediatric infectious disease or vaccine research. Interim results are planned to be shared with the JVCI and presented at the ESPID summer 2019 meeting with final results in 2020.

Participating families will be asked if they would like to receive a copy of the final report.

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