



RESEARCH CLINICS PROTOCOL

1 TITLE PAGE

Full/long title of study	Improving outcomes by addressing variation at the end of routine care for young adults born with cleft lip and/or palate
Short title/study acronym	Cleft@18-23
Protocol version number /date	1 01/10/2024
IRAS Number	345805
ISRCTN/Clinicaltrials.gov number	To be registered on ISRCTN
Sponsor	University Hospitals Bristol and Weston NHS Foundation Trust (UHBW).
Sponsor reference number	DE/2023/7534
Funder name and reference number (if applicable)	NIHR Programme Grant for Applied Research NIHR205006
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2 PROTOCOL VERSION HISTORY

Amendment No. State whether Substantial Amendment (SA) or Non- substantial amendment (NSA)	Version No.	Version Date	Brief summary of change(s) and reason for update.
Initial Application	1.0	01/10/2024	Not applicable

3 SIGNATURE PAGE

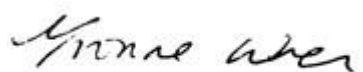
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirements.

I agree:

- to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor
- that no activity will commence at participating sites until Sponsor green light is confirmed
- that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature:



Date:

01/10/2024

Name (please print):

Yvonne Wren.....

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6 LAY SUMMARY

Cleft lip and/or palate is a lifelong condition affecting 1 in 700 births. From birth to early adulthood, individuals born with cleft lip and/or palate in the UK follow a care pathway from specialist regional cleft centres which includes input from a range of professionals including surgeons, speech and language therapists, specialist nurses, dentists and psychologists. Typically, they will be discharged from routine care between the ages of 15 and 25 but can come back to the regional cleft service at any stage.

Currently we do not know what variation there is in outcomes (i.e. how well individuals do in response to different NHS interventions) for young adults born with cleft lip and/or palate after they are discharged from routine care. This programme of research will determine whether outcomes vary depending on things like where they live, their biological sex or gender, or their ethnicity. Once we understand how outcomes vary, and the scale and type of variation, we will work with young adults born with cleft lip and/or palate and specialist clinicians to develop ways to ensure that everyone born with a cleft has the same opportunity to do well.

This programme has four research projects.

1. We will run research clinics with regional cleft centres across the UK to measure the patient and clinician reported outcomes of young adults born with cleft lip and/or palate relating to their well-being, appearance, speech, hearing, teeth, quality of life and level of educational attainment. We will use this information to report on the range of outcomes and how these vary for different groups based on characteristics such as ethnicity, socio-economic status, biological sex and gender and geographical location.
2. We will interview young adults with cleft lip and/or palate to understand how they describe their outcomes and any needs they have identified since being discharged.
3. We will ask the young adults born with cleft lip and/or palate and professionals who work in regional cleft centres what they consider to be a good outcome at the end of routine care.
4. We will work together, co-designing activities, to develop and try out a new type of intervention. This may consist of a tool in the form of an app or other web-based platform, which can provide support and strategies for this population after discharge from routine care.

We will consult with the Cleft@18-23 Patient and Public Involvement (PPI) group to determine the most impactful ways to share results from this research. This is likely to include publishing academic papers and presenting at conferences alongside the PPI group to reach people who can influence cleft care. We will also use a variety of methods to make the findings of this research available to participants and the wider cleft community. We will consult with and seek advice from our PPI group in these activities.

7 SYNOPSIS

KEY STUDY INFORMATION	
Study Title	Improving outcomes by addressing variation at the end of routine care for young adults born with cleft lip and/or palate
IRAS Number	345805
Study Design/Type	Multiple methods across four discrete studies within the programme: Cross-sectional cohort study; qualitative interviews; Delphi; co-design.
Study Participants	Young adults aged 18-23 years old born with cleft lip and/or palate
Planned Sample size	600 (aiming to recruit 640 as contingency for any missing data)
Planned Study Period	January 2025 to March 2027 (60 months)
End of study definition	Final report to funder.
Single site or multi-site	Multi-site
Research Aim(s)	What variation in outcomes exists for young adults born with cleft lip and/or palate at the end of routine care?
Research objectives	<p>Work package 1: Detailed in this protocol</p> <ul style="list-style-type: none"> To describe variation in clinical, psychosocial, educational and patient reported outcomes for young adults born with cleft lip and/or palate at the end of routine care. To identify associations between variations in outcomes and specific equality, diversity and inclusion characteristics, specifically geography (where people live), ethnicity, biological sex, gender, socio-economic status and health literacy. <p>Work package 2: Submission in future protocol amendment</p> <ul style="list-style-type: none"> To understand young adults' views of their outcomes and experiences to inform the development of an intervention to support this population. <p>Work package 3: Submission in future protocol amendment</p> <ul style="list-style-type: none"> To achieve stakeholder consensus on what constitutes a good outcome of cleft care at the end of routine care <p>Work package 4: Submission in future protocol amendment</p> <ul style="list-style-type: none"> To co-design and evaluate an intervention to support young adults born with cleft lip and/or palate and address variation in outcomes
Intervention(s) (if applicable)	To be determined following completion of work packages 1 and 2
Archiving period	All data will be stored indefinitely. Consent will be sought from participants to permit sharing of the pseudonymised data with other researchers who have obtained approval to use the data to address clinically relevant research

	questions. Consent will be sought from participants to permit storing of the personal data so that they can be contacted about future studies.
SAMPLES (If applicable)	Speech recordings will be collected for analysis as well as photos (2D and 3D) and videos and intra oral scans. No biological samples will be collected
DATA	<p>Joint Data controllers: University Hospitals Bristol and Weston NHS Foundation Trust and University of Bristol, Beacon House, Queens Road, Bristol, BS8 1QU</p> <p>Data Processors: University of Bristol, Beacon House, Queens Road, Bristol, BS8 1QU Newcastle University, Newcastle upon Tyne, Tyne and Wear, NE1 7RU</p> <p>Data Custodian: Professor Yvonne Wren University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8 2BN</p>

8 LIST OF ABBREVIATIONS

Abbreviation	Full text
CI	Chief Investigator
CLAPA	Cleft Lip and Palate Association
CRF	Case Report Form
EDI	Equality, Diversity and Inclusion
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File (This forms part of the TMF)
NHS	National Health Service
PI	Principal Investigator
PPI	Patient and Public Involvement
PIS	Participant Information Sheet
PSC	Programme Steering Committee
REC	Research Ethics Committee
R&D	Research and Development
SOP	Standard Operating Procedure
TMF	Trial Master File
UHBW	University Hospitals Bristol and Weston NHS Foundation Trust
UoB	University of Bristol
WP	Work Package

9 FUNDING

Funders	Financial and non-financial support given
NIHR Programme Grant for Applied Research, ref: NIHR 205006	Financial support of £1,978,946.79 for the programme of four related research projects

10 ROLES AND RESPONSIBILITIES

10.1 Role of sponsor and funder

The sponsor for the study will take responsibility for the quality and conduct of the study. A representative of the sponsor will be invited to attend the monthly co-applicant meetings, where they will have a standing item on the agenda for sponsor related activity. They will also be invited to attend the biannual Programme Steering Committee meetings. The CI and Programme Manager will also meet with a representative of the sponsor at regularly to discuss progress of the set up and management plan and recruitment activity as well as other relevant activity such as that relating to contracts and finance and any adverse events. Reports to the funder will be shared with the sponsor and any amendments requested by the sponsor will be discussed with the CI and agreed prior to submission to the funder.

The funder's role is to provide the finance but also to monitor the progress of the study according to the proposal. This is carried out via the Programme Steering Committee and the submission of annual reports.

10.2 Study team

The study team comprises the following individuals:

Chief Investigator: leads the team and is the main contact for the funder and sponsor. The CI takes primary responsibility for the conduct of the study at all participating sites. Working closely with the Programme Manager and the sponsor, they are responsible for ensuring that the study is delivered within budget, that processes for successful delivery of the study at participating sites are in place and that terms agreed in collaboration agreements are complied with. They are also responsible for ensuring effective communication with the sponsor and funder through regular meetings and submitted reports. With regards to the protocol, as CI they will ensure that sufficient information is provided in the protocol for the study to be effectively delivered with full compliance.

Programme Manager: provides operational management to the study, including budgetary control and overseeing human resources related activity. The Programme Manager will be the key point of contact for all participating sites and will coordinate the collation of all documentation relating to the study, including both internal documents for study team use only and external for submission to ethics, Health Research Authority approvals, funders etc.

Research Administrator: will provide administrative support throughout the study and will be a point of contact for participants and potential participants.

Database Manager: will establish the systems necessary for collection of data from the research clinics and ensure processes for ongoing data management and security as well as access.

Work Package leads: Each work package lead is responsible for planning and delivery of the work outlined in their work package on the funding application form. This proposal is describing the planned research for work package 1.

Senior Research Associates: will work together to deliver the research outlined in this proposal. They will liaise with the sites and ensure processes for running the Cleft@18-23 Research Clinics are in place. They will also attend the clinics to facilitate them on the day and lead the collection of data.

Patient and Public Involvement representatives: are individuals with lived experience of cleft who are representing the patient community in the plans for the study. The CEO of the Cleft Lip and Palate Association, CLAPA) provides a broader view in their role representing all those affected by cleft lip and/or palate.

Other co-applicants: all contribute to the running of the study through regular monthly co-applicant meetings and commenting on plans specific to their area of speciality.

Health economist: works on the health economic aspects of the study.

Statistician: will work on the statistical analysis of data collected in the Cleft@18-23 Research Clinics.

10.3 Trial/study management committees/groups and individuals

The study is supported by a Programme Steering Committee (PSC) comprised of a chair (Dr Tim Peakman) with experience of chairing large programmes of research. Other members are Prof Heather Cordell (Medical Statistician), Mark Edwards (adult with lived experience of cleft), Dr Kate Le Marechal (Clinical Director of regional cleft service and consultant clinical psychologist in cleft) and Dr Ginette Phippen (Chair of the UK national Cleft Development Group which oversees cleft care in the UK). The PSC meet twice yearly and include representatives from the funders and the sponsors at each meeting together with the CI, the Programme Manager and other key individuals from the study team as needed.

The study is guided by the Cleft@18-23 PPI Group. More information about this group is available at <https://www.bristol.ac.uk/dental/research/epidemiology-health-services-research/cleft18-23-study/patient-and-public-involvement/>. This group is chaired by PPI co-applicant Alex Hennessey and began with three core members. Recruitment to this group is ongoing. A schedule of meetings is planned, and members will be offered £25 per hour for the time they are involved in the study.

10.4 Protocol Contributors

The protocol has been written by the study team with particular involvement of the senior research associates, work package leads, the CI and programme manager. Input to key sections has been included based on PPI activity and our PPI partners have reviewed and amended the Participant Information Sheet (PIS), the consent form and the promotional and recruitment materials. The protocol has been reviewed by representatives of the sponsor.

11 KEY WORDS

Cleft lip and/or palate; young adult; outcomes; multidisciplinary; protected characteristics; equality, diversity and inclusion

12 BACKGROUND

Cleft lip and/or palate (CL/P) is one of the most common congenital anomalies, frequently resulting in multiple far-reaching adverse outcomes across the lifespan. These include visible difference in the face, speech difficulties affecting intelligibility, with potentially lower educational, vocational, social, mental and physical health outcomes compared to peers. Prevalence varies with geography, ethnicity and socio-economic status and this health inequality extends to quality of care with a call for research to investigate this.

Affecting over 1000 babies in the UK each year, initial corrective surgery takes place usually in the first year of lifeⁱ. On average, children born with clefts have 3.2 admissions and spend 13.2 days in hospital in the first two years of lifeⁱⁱ. Thereafter these children attend numerous clinical appointments with a multi-disciplinary team (MDT) comprising speech and language therapists (SLT), audiologists, dentists, orthodontists, psychologists, specialist nurses and surgeons over a 20-year period; they may undergo multiple operations. Once the young adult has completed scheduled interventions (typically between the ages of 15 and 25), they transition from a care pathway structured around routine appointments, regular follow-up, and audit, typically facilitated via parents, to a system of on-request care driven by the young person themselves.

In two focus groups carried out with ten young adults born with cleft lip and/or palate aged 16-20, they told us they find this transition in responsibility for, and ownership of, care difficult to navigateⁱⁱⁱ. Our focus groups revealed transition coincides with other challenges to mental health and self-confidence as individuals start work or move away from home.

Young adults born with cleft lip and/or palate attending the focus groups added that concerns about appearance can increase in young adulthood together with worries about speech and hearing, sometimes leading to feelings of isolation.

Additional intervention from surgeons, orthodontists, psychologists and other members of the MDT is an option to address many of these concerns. However, decisions about treatment are now their responsibility and this can be overwhelming.

Young adults born with cleft lip and/or palate are keen to feel in control of their cleft care but are unsure who to ask for help. They find cleft clinic appointments difficult to manage, with the focus on clinicians' queries and concerns rather than their own, while contact with GPs can lead to referrals to generic rather than specialist services^{iv}. These issues can result in wasted time for patient and clinician.

Regional cleft specialist teams have acknowledged that variation exists in services with the suggestion that outcomes for young adults born with cleft lip and/or palate at transition may differ between sub-populations, including those identified by equality, diversity and inclusion (EDI) characteristics. Specifically, concerns about variation by geography, ethnicity and socio-economic status were raised. Our focus group with young adults born with cleft lip and/or palate identified concerns that young men were less likely to access support than young women.

The development of this protocol has been informed by a series of focus groups with each of the core disciplines involved in cleft care (surgeons, dentists, orthodontists, speech and language therapists, psychologists, nurses, audiologists) and two focus groups with young people aged 15-20 born with a cleft of the lip or palate. The protocol was further refined with input from all 16 regional centres following visits to each centre by the CI, prior to the start of the study funding period and by our PPI partners in this programme of work.

13 RATIONALE

We need to determine if variation in outcomes exists for this population as currently no outcome data are collected at the end of routine care and care pathways centre around variation in outcomes that are measured at age 5. This is at least 10, and sometimes 20 years before a patient is discharged. If the variation which exists for subpopulations based on EDI characteristics is considered reasonable to expect (i.e., within a given range), then there will be no need to develop an intervention. The first step is to collect data on outcomes following discharge from routine care across the range of areas impacted by being born with cleft lip and/or palate. With these data, it will be possible to determine what variation exists in outcomes and whether the level of variation observed is considered acceptable (i.e., within a given range). Statistical analysis will determine whether the variation can be explained by factors relating to where in the country individuals have received their cleft care and protected characteristics including ethnicity, biological sex and gender, and socio-economic status.

This is the activity which will take place in Work Package 1. The current version of the Protocol is focused on Work Package 1. Amendments will be submitted for the remaining three work packages closer to the time when they are due to be delivered.

The data on outcomes will be collected through a series of research clinics that will take place at the NHS regional cleft centres across the UK. Outcome data will be collected for the key domains of well-being, appearance, facial growth, speech, hearing, oral health, patient satisfaction and educational attainment. The four work packages planned in the Cleft@18-23 Research Programme as summarised in table 1.

Table 1: Summary of Work Packages in Cleft@18-23 Programme

Work Package (WP)	Activity	Purpose
1	Research Clinics	Collect data on outcomes and analyse variation
2	Interviews	Explore experiences at end of routine care
3	Delphi study	Reach consensus on good outcomes
4	Co-design	Develop and evaluate an intervention

14 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

14.1 Primary objective

- To describe variation in clinical, psychosocial, educational and patient reported outcomes for young adults born with cleft lip and/or palate at the end of routine care (WP1)

14.2 Secondary objective(s)

- To identify associations between variations in outcomes and EDI characteristics, specifically geography (where people live), ethnicity, biological sex, gender, socio-economic status and health literacy (WP1)

- To understand young adults' views of their outcomes and experiences to inform the development of an intervention to support this population (WP2)
- To achieve stakeholder consensus on what constitutes a good outcome of cleft care at the end of routine care (WP3)
- To co-design and evaluate an intervention to support young adults born with cleft lip and/or palate to address variation in outcomes (WP4)

14.2.1 Outcome measures/endpoints

The Cleft@18-23 Research Clinics will collect data on outcomes from routine clinical care for the population of young adults who were born with a cleft lip and/or palate. The outcomes will cover several domains including well-being, appearance, facial growth, speech, hearing, oral health, and patient satisfaction. Data on educational attainment will be obtained via linkage with the National Pupil Database held by the Office for National Statistics.

Each participant will attend a single Research Clinic with no requirement to return for follow-up as all data will be collected during that one point of contact.

14.2.2 Primary outcomes

The primary outcome to be collected and used in statistical analysis relates to well-being. This domain was selected based on a unanimous decision from representatives of all disciplines involved in cleft care and the patient community during the focus groups which preceded the current research. This is consistent with systematic reviews^{v,vi,vii,viii,ix} which concluded that psychosocial functioning is a major predominant concern at transition to adult care for young adults born with cleft.

The 'Limitation in usual role activities because of emotional problems' subscale from the Short Form36 (SF36)^x will be used as the primary outcome measure. This subscale is equivalent to the Mental Health Index (MHI-5)^{xi} which has been used in isolation from the rest of the scale. The SF36 is a health-related quality of life measure which encompasses a biopsychosocial approach to health outcomes. It includes subscales for limitations on physical, social and usual activities due to health, physical or emotional problems as well as a subscale on general mental health and general health perceptions. It is therefore suitable for the wide range of impacts experienced by young adults born with cleft lip and/or palate, over and above oral health, and for those at risk of multiple long-term conditions.

14.2.3 Secondary outcomes

Data from a range of secondary outcomes will be collected using tools which have been selected carefully with clinician and patient involvement. The specific tools have also been identified because of their capacity to provide consistent measures of the outcome of interest. The secondary outcome domains are appearance, facial growth, speech, hearing, oral health, and patient satisfaction. Details on the specific tools used for data collection and analysis relating to these outcomes are detailed in the sections below.

15 STUDY DESIGN AND SETTING

15.1 Study design (Work package 1)

Cleft@18-23 Research Clinics is a multi-centre cross-sectional cohort study. Recruitment will begin in January 2025 with the clinics and data collection planned to end in March 2027.

Participants will attend a Research Clinic at one of the regional cleft centres in the UK for approximately 3 hours. During this time consent will be checked and participants will be asked to: answer self-report questionnaires on electronic tablets provided by the study; see a medical photographer for photographs of their face and nasolabial area as well as their teeth and oral cavity; complete a hearing screen; record a sample of speech with the speech and language therapist; and see a dental therapist/hygienist who will measure dental health and perform an intra-oral scan of the mouth. They will also have the opportunity to speak to a clinical psychologist or experienced cleft clinician or other trained health professional at the end of the clinic if they want to. This is not part of the research, and no data will be collected from this contact, but is being made available in the event that the research clinics raise any issues for them which they would like to talk to somebody about.

15.2 Study setting

Cleft@18-23 Work Package 1 is a multi-site project, conducted in collaboration with the UK Cleft Centres, as shown in the map in Figure 1 and in table 2 below.

Figure 1: Map of all UK Cleft Centres



Table 2: List of all UK Cleft Centres

Cleft Service	Surgical Hub Sites
Scottish Cleft Network	Royal Hospital for Sick Children, Glasgow
Northern and Yorkshire	Royal Victoria Infirmary, Newcastle-upon-Tyne
	Leeds General Infirmary, Leeds
North Wales and Northwest	Alder Hey Children's Hospital, Liverpool
	Royal Manchester Children's Hospital, Manchester
Trent Regional Cleft Service	City Hospital, Nottingham
West Midlands Cleft Lip and Palate Service	Birmingham Children's Hospital, Birmingham
Cleft Net East	Addenbrooke's Hospital, Cambridge
South Thames	Evelina Hospital, London
North Thames	Great Ormond Street Hospital, London
	Broomfield Hospital, Chelmsford
Spires Cleft Centre	John Radcliffe Hospital, Oxford
	Salisbury General Hospital, Salisbury

South Wales and South West	Morrison Hospital, Swansea
	Bristol Dental Hospital, Bristol
Northern Ireland	Royal Belfast Hospital for Sick Children, Belfast

The populations served by these centres are large and varied but also differ in terms of ethnicity and levels of deprivation. This will help with reaching a diverse sample of potential participants. See screening section for how a diverse and representative group of participants will be achieved.

16 PARTICIPANT ELIGIBILITY CRITERIA

Broad inclusion criteria will be applied such that young adults aged 18-23 years with any cleft subtype, with or without an identified syndrome and additional needs, will be eligible. As the aim for Cleft@18-23 is to look at outcomes from the UK cleft care pathway it is necessary to exclude anyone who has received all or part of their care outside of the UK.

16.1 Inclusion criteria

- Born with a cleft of the lip or palate or both (including microform cleft lip and submucous cleft palate)
- Initial cleft repair carried out in UK prior to age 2 years
- Cleft care continued in UK since the primary repair
- Aged between 18 and 23 years at time of recruitment
- Completed routine cleft care more than 6 months ago
- Ability to give informed consent

16.2 Exclusion criteria

- Received some, or all, of their treatment outside of the UK

Those not eligible to participate will be offered the opportunity to participate in PPI activities and/or other related projects in the programme or in future research that the applicant team are involved in as they are developed.

16.3 Equality, diversity and inclusion considerations

The prevalence of cleft lip and/or palate is higher in some Asian populations (Far East, South and South East) and lower in those with African heritage^{xii}. Some outcomes from treatment have been negatively associated with non-white ethnicity and deprivation^{xiii}.

Guidance from the NIHR INCLUDE Ethnicity Framework and the Centre for Ethnic Research will be followed to ensure the study design is inclusive and the demographic characteristics of the sample reflect the patient population. We will refer to the guidance on Equality Impact Assessments^{xiv} to determine how the Cleft@18-23 Research Clinics might impact on individuals with a range of protected characteristics differently.

We do not anticipate translation services will be required because eligibility for the study will be for care to have been received by one of the UK regional cleft teams from primary surgery prior to school entry to the point of recruitment at age 18-23 years.

We will use guidance from the NIHR INCLUDE Project and the NIHR EDI Toolkit^{xv} to ensure representation of under-served groups in the sample and will work with CLAPA to recruit widely. We will also access support from the Centre for Ethnic Health Research at the University of Leicester and use a Health Literacy Survey to measure variation in participants' ability to access health information which could impact on their care and unmet needs at transition.

17 STUDY PROCEDURES

17.1 Recruitment

Summary: Potential participants will be made aware of the study through one of four routes. Each of these routes will provide a QR code or URL link to the study where more information is available and where there is an option to click a link to complete an 'Initial Expression of Interest Contact' form which will be sent to the study team. Voluntary online completion of the 'Initial Expression of Interest Contact' form by the potential participant will be accepted as implied consent for the information to be collected, reviewed and for them to be contacted by the study team. The form will help the study team to determine eligibility and manage the sample so that data are collected from a sample population which represents the UK cleft population across various key characteristics (cleft subtype, biological sex, ethnicity, socio-economic status). If a potential participant completing the form is eligible and also fulfils criteria relating to characteristics required for recruitment to specific identified groups, then they will be contacted by a member of the study team. The member of the study team will outline the plans for the research clinic and go through the consent form. The study team member will take verbal consent from the potential participant if they wish to continue. This marks the point at which an individual is recruited as a participant. A link to an electronic consent form will be sent to them (or a paper copy if they request one) and this will be checked at the research clinic by a member of the Study Team with GCP training. More detail on this process is provided below.

Cleft lip and/or palate is sometimes associated with additional diagnoses or syndromes. As with the general population, there is a possibility that some of these young adults may have learning difficulties. This may make it more difficult for them to understand the information sheet, consent form and to complete the initial contact form and consent form. There will be an easy read version of the participant information sheet to help with this and we will also involve a carer, parent or trusted friend to read and discuss this with them. If there are concerns that the young adult does not have capacity to consent for themselves then they will not be able to take part in the Research Clinic. They will need to be able to consent for themselves and be able to respond to the questionnaire for themselves, however help can be provided to read and assist with response recording (not decision making).

The four routes through which a potential participant will hear about the study:

1. Regional Cleft Centres
2. Cleft Lip and Palate Association (CLAPA)
3. Social media and advertising campaigns
4. Prior Cleft Care UK^{xvi} study participation

The four routes have been planned to maximise the sharing of information about the study. Regional Cleft Centres and Cleft Care UK study participants will be reached via the last known postal address of the parents. CLAPA will be able to share information directly with their groups (especially the newly formed young adults' group) and the social media and advertising campaigns will reach young adults more widely.

Documents to assist in promoting the study have been developed and comprise a poster, post for use in social media and a flyer. These materials will explain that those participating in the study will be paid £50 and will have their travel expenses covered. A description of how these will be used in the recruitment process is described below for each method of recruitment and summarised in the Recruitment Flowchart. Documents for use directly in recruitment comprise the invitation letter, the Participant Information Sheet (PIS), the accessible PIS, the 'expression of interest' Initial Contact Form and the Consent Form. To support recruitment, we will also record a video about the Cleft@18-23 Research Clinics and the benefits of being involved which will be developed and filmed with our PPI group and CLAPA.

Route A – Regional Cleft Centres

Regional Cleft Centres will identify patients who have been discharged from their cleft service and are aged 18-23 years old (See Section 17.1.1 below). Cleft Centres will be provided with:

- A poster for display in the Cleft Centre waiting room
- A site file
- Printed flyers for people to take from the Cleft Centre waiting room and for distribution in direct mailing (see below)
- Printed invitation letters
- Pre-paid envelopes
- A spreadsheet to complete to assist with documenting who they have sent information to and when a follow up is needed

Staff from each cleft centre will be asked to add the potential participant's name to the letter and then place the letter and flyer in the stamped envelope and add the address before placing in the post. All staff involved will be NHS staff who understand the importance & need for confidentiality. They will receive training in the research protocol and processes for sharing information with potential participants by the study team. They will not be receiving consent.

The process for recruitment is as follows:

1. A member of the cleft team sends the Cleft@18-23 recruitment flyer and the invitation letter to the last known address of all eligible young adults who have been discharged from their service.

The flyer has an electronic link in the form of a QR code to the study website. Those interested to know more will scan the QR code. This will include an overview of the study aim and brief details about the Research Clinic. It will also contain links to the PIS, easy read PIS, the recruitment video, and an initial 'expression of interest' contact form. The initial contact form will also serve as a screening form for the study team to monitor recruitment and identify groups who are at risk of under-representation. This information will be used to

develop targeted approaches to promoting the study and recruitment to ensure the final sample is representative of the population.

Potential participants may request the information on paper or another alternative format via contact details on the introductory letter. If requested, the study team will send out paper versions of the PIS, easy read PIS and initial contact form with a pre-paid addressed envelope for return to the study team. Alternative formats of the recruitment materials will be considered in response to requests for these. It is not anticipated that there will be requests for materials in other languages as criteria for inclusion is that cleft care, from primary surgery in early childhood to discharge from the cleft service, has taken place in the UK. Therefore, the participants' schooling will also have been completed in the UK and in English.

2. The Cleft@18-23 study team will notify the local cleft centre team via an encrypted email or phone call two weeks after letters have been sent out to let them know who has responded. The cleft centre team will follow up those who have not responded with a phone call where possible to check whether the potential participant has seen the flyer and knows about the study. Where phone numbers are available, these may be for the potential participants' parents.
3. Potential participant completes the initial contact form indicating their interest in taking part and their consent for the study team to contact them. The study team will check the initial contact form & enter information on to a screening spreadsheet which will be used to monitor recruitment and ensure the final recruited sample is representative of the UK cleft patient population in terms of cleft subtypes and demographic variables (see Section 17.1.2 below).
4. A member of the study team will contact the potential participant using their preferred method of contact as indicated in the Initial Contact Form. They will discuss what is involved in taking part in the research clinic and the contents of the Consent Form to ensure that the potential participant is happy to give consent to the compulsory elements. They will discuss whether they need any assistance to get to the research clinic or any support during the clinic itself (e.g. with completion of self-report questionnaires, with mobility, with chaperoning for the medical photography, speech and hearing, or dental elements of the clinic). If the potential participant is happy to give verbal consent to participate in the research clinic, then a date and time will be confirmed with the participant at one of the cleft sites which is reasonable for them to travel to. An Appointment Letter will be sent to the participant with the details of the date, time and location of their appointment at the research clinic and a link to the electronic consent form (or a paper copy if this has been requested). This information will be shared with them using their preferred method of contact, but a paper version will also be sent via post. They will be asked to bring this paper version to the hospital when they attend the clinic. This is to assist them in finding the location of the research clinic in the event that they need to ask for help from anyone working in the hospital setting but not involved in running the clinic.

OR

A member of the study team will contact the potential participant using their preferred method of contact to thank them for their interest in taking part and to explain that they

have been placed on a reserve list for a clinic and the reason for this. This will happen when we have already recruited a sufficient number of participants for a given set of criteria based on cleft subtype, geographic region, biological sex, ethnicity, socioeconomic status (See Section 17.1.2 below). Those placed on a reserve list will be contacted in the event that a participant withdraws from the study. There will also be opportunities for those on the reserve list to be involved in other elements of the programme (Work Packages 2, 3 and 4) or in other studies which the study team may be involved in at some stage in the future if they agreed to this in the Initial Contact Form.

OR

A member of the study team will contact the potential participant using their preferred method of contact to thank them for their interest in taking part and to explain that they are not eligible to participate in this research. This will happen when they don't meet all of the inclusion criteria. However, there will be an opportunity for those not eligible for the clinics to stay informed of other studies which the study team may be involved in at some stage in the future if they agreed to this in the Initial Contact Form.

5. One week prior to the research clinic date, a member of the study team will contact the participant to revisit the information about the clinic and what will happen and confirm that they are still planning to come. This will be an opportunity to confirm travel plans and address any potential challenges to these.
6. One to three days (allowing for a weekend) prior to the research clinic date, a member of the study team will contact the participant again to remind them of the date and time and to confirm their intention to attend.
7. The potential participant arrives at the clinic. A member of the study team will go through the Consent Form and checked that it has been completed correctly.

Route B: Cleft Lip and Palate Association (CLAPA)

CLAPA will assist with sharing information about the Cleft@18-23 Research Clinics. This will be done in a variety of ways including via:

- a. CLAPA voices – their PPI group
- b. The 'latest research opportunities' section on their website
- c. Facebook groups for parents & carers (for awareness), adults and young people
- d. Posts on their social media channels including Facebook, X (formerly Twitter), Instagram and YouTube
- e. Their monthly e-newsletter
- f. Direct communication with young adults who have indicated to them that they are interested in taking part in research

For points a-e above, CLAPA will share the flyer or social media posts as detailed in route C below.

When communicating directly with young adults who have expressed an interest in research, CLAPA will send the Cleft@18-23 flyer via the method in which they usually communicate with the young adults. The Cleft@18-23 study team will notify CLAPA via encrypted email or phone call two weeks after letters have been sent out to let them know who has responded. CLAPA will follow up those

who have not responded with a phone call where possible to check whether the potential participant has seen the flyer and knows about the study.

The process will then be followed as for Route A – Regional Cleft Centres, points 3 to 7.

Route C: Social media and advertising campaigns

To raise awareness of the Cleft@18-23 study, we will run a campaign using paper and electronic versions of the Posters, which will be distributed to further and higher education institutions as well as other places identified as having high frequency of young adults in attendance, and social media. The posters and social media posts will contain a URL link or QR code to the recruitment page of the study website.

Those interested in knowing more can click on the link or scan the QR code for more information. The process will then be followed as for Route A – Regional Cleft Centres, points 3 to 7.

Route D: Cleft Care UK Study

Those families who participated in Cleft Care UK and who gave consent to be contacted about future studies will be sent a letter about the Cleft@18-23 study, together with the flyer. Those interested in knowing more can click on the link or scan the QR code for more information. The process will then be followed as for Route A – Regional Cleft Centres, points 3 to 7.

17.1.1 Participant identification

The primary route for identifying potential participants will be via the UK cleft centres (Figure 1). The staff in the centres will be asked to identify eligible participants using the inclusion and exclusion criteria outlined above (16.1 and 16.2).

Potential participants may also see information about the study via CLAPA, social media and advertising or from the study team if their parents consented to being contacted when they took part in Cleft Care UK.

17.1.2 Screening

To enable the study team to recruit a diverse group of young adults that best represents the cleft population to each Cleft@18-23 Research Clinic, an initial contact form will be completed by potential participants, with information from this entered on to a screening matrix by the study team.

The initial contact form will explain the need for the information requested and will then ask questions about the potential participants. Some of the questions are to determine eligibility (those marked with *) and some are to assist with establishing a sample which is representative (those marked with **). Other questions (no asterisk) are asked for the purpose of communicating with the potential participant or describing the sample:

- Contact details

- Age (18-23yrs) *
- Age when they had their primary surgery* (less than or at 2 years old/Over 2 years old)
- Sex at birth (Male/Female/prefer not to say) **
- Gender they identify as (We are not going to use this information for eligibility or representativeness but if we do not ask it, those for whom this is particularly important may feel that they have not had the opportunity to express this aspect of their identity.)
- Cleft lip &/palate sub type** (Cleft lip only, cleft palate only, unilateral cleft lip & palate, bilateral cleft lip & palate, microform cleft lip, submucous cleft palate, other)
- Ethnicity** (Asian/Asian British; Black/African, Black/Caribbean, Black British; Mixed/multiple ethnic groups; Other; White). Each of these categories are broken down further and an option is given for them to write a response themselves.
- First 4 letters/numbers of their postcode when they were doing their GCSEs**.
- First 4 letters of their postcode now**
- Cleft centres where they have received their care** - list of all, tick all that apply

We will use data from the Cleft Registry and Audit Network (CRANE) Database (a registry which collects information about all children born with cleft lip and/or cleft palate in England, Scotland, Wales, and Northern Ireland) together with the Office of National Statistics Census data to determine targets for recruitment across each of these characteristics.

17.1.3 Targeted Approaches to Recruitment

The screening matrix will be reviewed regularly by the study team, and if groups of people are not well represented in the participant sample, a more targeted approach to reach these groups will begin. This would include asking our PPI group to help with ideas and sharing the Cleft@18-23 information more widely, asking direct contacts in relevant community and religious organisations and social prescribing coordinators to target specific populations. New processes or documents which are developed through this process will be submitted as an amendment.

When we receive interest from individuals who are already well represented in the sample (i.e. quota has been filled), they will be informed that they will be placed on a reserve list. They will be contacted if a space becomes available (i.e., someone else withdraws from the study) and will also be invited to participate in other studies within the programme or related to it. (See section 17.1 above).

17.2 Payment

Participants will be offered £50 shopping vouchers at the end of the Cleft@18-23 Research Clinic investigations as a thank you for the time and effort made to participate.

We will also share information about how to claim reimbursement for their travel expenses. Once a date and time for the participant to attend a Cleft@18-23 Research Clinic has been confirmed and the consent form has been discussed, the study team will discuss travel arrangements for reaching the clinic with the participant. We know that some of our potential participants will have learning needs or difficulties. Where necessary, and in discussion with any carers involved, we will assist in the arrangement of travel.

17.3 Informed consent

The Consent Form will be discussed with the participant following receipt of the initial contact form to gather verbal consent for the clinic activities. An electronic (or paper copy if requested) of the Consent Form can be completed prior to the clinic and will then be checked on arrival at the clinic with a GCP trained member of the study team.

Consent will be sought for (all required unless stated as optional):

- Participation in the clinic investigations
- Completion of the self-report forms
- Collection of 2D and 3D images and video recording with speech
- Access to participant records held at the cleft centre and national NHS records
- Access to participant educational records
- Access to CRANE data (if applicable)
- Permission to keep participant contact details to let them know about future, relevant research including the other work packages in Cleft@18-23 (optional)
- Permission to share their data with other approved researchers to address clinically relevant research questions (optional).

The participant remains free to withdraw at any time from the study without giving reasons and without prejudicing their further treatment. There is information and a contact point for this on the participant information sheet. See section 17.6 to read more about the study withdrawal criteria.

Cleft lip and/or palate is sometimes associated with additional diagnoses or syndromes. As with the general population, there is a possibility that some of these young adults may have learning difficulties. This may make it more difficult for them to understand the information sheet, consent form and to complete the initial contact form and consent form. There will be an easy read version of the participant information sheet to help with this and we will also involve a carer, parent or trusted friend to read and discuss this with them. If there are concerns that the young adult does not have capacity to consent for themselves then they will not be able to take part in the Research Clinic. They will need to be able to consent for themselves and be able to respond to the questionnaire for themselves, however help can be provided to read and assist with response recording (not decision making).

17.4 Trial assessments

17.4.1 Baseline data

On arrival at the clinic, the participant will be greeted by one of the clinic facilitators (either a member of the study team or a member of the local clinical team) who will outline the activities planned during the clinic. Their identity (name and date of birth) will be checked. Consent will be re-checked with a member of the study team with GCP training.

The participant will be given a Case Report Form and a large card containing their Study ID number (comprising [2-digit code representing clinic site] + [3-digit unique patient identifier from 001 to 640]). The Case Report Form will be used at each station in the clinic for those collecting data to record the elements of the clinic which have been completed. The large card will be used in all photographs and videos so that the study ID for the participant is visible on playback.

The participant will then be guided through the following five stations in the research clinic:

1. Self-Report Questionnaires Part 1
2. Medical Photography
3. Speech and Hearing Assessment
4. Dental Examination
5. Self-Report Questionnaires Part 2

Station 1: Self-Report Questionnaires Part 1

The self-report questionnaires will be presented electronically through the REDCap (a secure web application for building and managing online surveys and database) and Concerto (an adaptive testing platform developed and maintained by the University of Cambridge Psychometrics Centre). Participants will be provided with part 1 of the self-report questionnaire to complete on an electronic device (tablet). Paper versions of the questionnaire will be available if preferred by participants. It is anticipated that completion of the Self-Report Questionnaire part 1 will take approximately 20 minutes. If a participant has learning difficulties, they can have a friend, carer, parent or member of the study team to help read the questions and record their responses. The person providing assistance cannot answer on behalf of the participant. It needs to be the participants' own views and responses.

The questionnaire comprises the following:

A. *General demographic information*

- a. Age - in years
- b. Sex at birth – dropdown menu
- c. Gender – dropdown menu
- d. Ethnicity – dropdown menu
- e. Parental Employment
- f. Cleft subtype, syndromic status and other conditions –multiple dropdown menus
- g. Cleft surgical history – number and type of operations

B. *CLEFT-Q* (Computerised Adaptive Testing (CAT) Version)^{xvii} will be used to measure participants' self-perception of the:

- a. Appearance of the Face
- b. Appearance of the Lips
- c. Appearance of the Nose
- d. Appearance of the Nostrils
- e. Appearance of the Jaws
- f. Appearance of the Teeth
- g. Appearance of the Cleft Lip Scar
- h. Psychological Function
- i. Social Function
- j. Speech Distress
- k. Speech Function
- l. Eating and Drinking

The CAT version of this tool typically takes seven minutes to complete.

C. Short Form-36 (SF-36)^{xviii}

We will use the five questions of the emotional role subscale of SF-36, also known as Mental Health Inventory (MHI-5) as the primary outcome measure of participant well-being.

D. Patient Health Questionnaire-8 (PHQ-8)^{xix}

This eight-item scale (PHQ-8) will be used to measure the outcome of depression in the participants and enable comparison with an unaffected population.

E. Generalized Anxiety Disorder (GAD-7)^{xx}

The score from the seven-item GAD-7 will be used to measure anxiety in the participants.

F. Health Literacy Population Survey Questionnaire (HLS19-Q12)^{xxi}

The HLS 19 -Q12, is a 12-item short form questionnaire derived from the HLS19-Q47 questionnaire. It will be used for measuring health literacy in the research participants. This information will be important to determine if outcomes are impacted by health literacy, defined by the NHS as the personal characteristics and social resources needed for individuals and communities to access, understand, appraise and use information and services to make decisions about health' [Health-literacy-how-to-guide.pdf \(library.nhs.uk\)](#) .

G. Connor-Davidson Resilience Scale (CD-RISC-10)^{xxii}

The 10-item CD-RISC-10, derived from the 25-item CD-RISC-25, will be used to measure stress coping ability in the participants.

Scores from each measure will be available for statistical analysis immediately following completion of the self-report questionnaire.

Station 2: Medical Photography

A local medical photographer will be present on-site to take 2D and 3D images.

Equipment required for this station is detailed in table 3. It is anticipated that the collection of image data will take approximately 20 minutes.

Table 3: Equipment for Cleft@18-23 Research Clinic Station 2: Medical Photography

Equipment	Taken to site by Study Team	Provided by Local Site
Plain white or black background		X
Full frame sensor digital SLR camera		X
100-105mm 1:2.8 lens		X
Macro ring-flash units		X
3D camera	X	
SD card	X	

- A. The 2D images will comprise the Core and Optional views for audit detailed in the Institute of Medical Illustrators (IMI) guidelines^{xxiii} for cleft lip and palate. Images will be stored on SD cards and uploaded to a secure server at the University of Bristol.

Outcome measures from the 2D images will be generated after the research clinic using a web-based human scoring system to produce a score comparable to an Asher McDade^{xxiv} Likert score from 1 to 5 where 1 is the better outcome for nasolabial appearance. The Dental Aesthetic Index will be used to generate clinical outcomes for dental appearance^{xxv}. Objective systems involving eye tracking and convoluted neural networks are in development as well as methods for measuring scarring and may also be able to be used when the image data are available. These will provide a more robust measure of clinical outcome for nasolabial appearance.

- B. The 3D Camera will be used to capture 3D images as per manufacturer instructions. The images will be taken in natural head position. The 3D images will be generated using specialist software and processed using recognised protocols. Images will be stored on the 3D software only accessible on registered devices by the research team and uploaded to a secure server at the University of Bristol.

Whole facial shells will be generated for analysis. Recognised protocols, mathematics and statistical techniques will be used to analyse the differences in facial shape. The camera software will compute a volumetric measurement for regions of interest (ROI) such as the whole face, the upper face (including cheeks), the nasolabial region and the mandible. These measures will be used in the statistical analysis.

Station 3: Hearing and Speech Assessment

A local speech and language therapist or speech and language therapy assistant will be on site to facilitate the hearing assessment and carry out the speech assessment. The equipment needed for station 3 is summarised in table 4. It is anticipated that the collection of hearing and speech data will take approximately 20-30 minutes.

Table 4: Equipment for Cleft@18-23 Research Clinic Station 3: Hearing and Speech Assessment

Equipment	Taken to site by Study Team	Provided by Local Site
HearScreen Smartphone hearing screening solution	X	
The Great Ormond Street Speech Assessment (GOS.SP.ASS) sentences and picture book	X	
High-definition video camera	X	
SD card	X	
Lapel microphone	X	
Headphones	X	
Tripod	X	
Audio recorder for backup (Tascam DR-05X)	X	

- A. Hearing levels will be screened using a pure tone hearing screen. We will use the hearScreen® from hearX ([hearScreen® by hearX Group - Smartphone hearing screening solution](#)). This screen provides a reading for each ear across a range of frequencies using calibrated over-ear headphones and software via a Samsung Galaxy smartphone. It takes 5-10 minutes and has been validated for use outside of audio booths^{xxvi,xxvii,xxviii,xxix}. Participants will be instructed by the SLT to place the headphones over their ears. The SLT will play tones via the smartphone at each of the following frequencies at a 35dB level: 500hz, 1000hz, 2000hz, 4000hz, 8000hz. The participant will indicate when they have heard a tone by raising their hand and the SLT will record this via the smartphone. Personal information can be pseudo-anonymised using the study ID number. Pass or fail at the following frequencies will be recorded on the Case Report Form. Results can be uploaded to hearX's secure cloud storage. Indications of hearing within normal limits or a loss at different frequencies will be indicated by the screening procedure for both ears. Variables based on these results will be generated for use in statistical analysis.
- B. A standardised speech sample will be collected using high quality audio and video recordings in a quiet room with the subject facing natural light if possible. Each participant will sit in front of a pale neutral background. A lapel microphone will be used. The face and upper neck will be framed in the picture. Following data collection, the speech and language therapist/speech and language therapy assistant will check, using headphones, that a high-quality sample has been recorded. The sample takes approximately 15 minutes and will

follow the protocol used in the Great Ormond Street Speech Assessment (GOS.SP.ASS)^{xxx}. This includes the following:

- Connected speech sample of approximately two minutes using a picture description task
- Rote speech including counting from 1-20 and 60-70
- Reciting the days of the week
- Repetition of the 16 GOS.SP.ASS sentences

The audio and video recordings will be transferred as soon as possible from the SD card to the secure server following the clinic and stored on a secure server at the University of Bristol. These will be pseudo-anonymised using the participant study number. Once securely stored the recordings can be deleted from the SD card.

Following the Research Clinic, two specialist cleft speech and language therapists will carry out consensus listening to the speech samples and rate them following the Cleft Audit Protocol for Speech – Augmented (CAPS-A)^{xxxii}. It will take 15 minutes per participant to complete the CAPS-A. Where there is no consensus between the two listeners, a third specialist SLT who is a member of the research team will also be called upon for an opinion. The CAPS-A will generate data on resonance, nasal airflow, passive cleft speech characteristics (CSCs), active CSCs and intelligibility.

From this data we will create the following variables for statistical analysis:

- Intelligibility on a five-point scale
- Velopharyngeal composite (VPC) score on a three-point scale (competent, marginally incompetent, incompetent)^{xxxii,xxxiii}
- Absence / presence of active CSCs in three categories: anterior, posterior, non-oral
- Percent Consonants Correct (PCC) measure (continuous variable)

Station 4: Dental Examination

The study dental therapist/hygienist will be on site to carry out the dental examination. The equipment required for station 4 is summarised in table 5. It is anticipated that the dental examination will take approximately 20 minutes.

Table 5: Equipment for Cleft@18-23 Research Clinic Station 4: Dental Examination

Equipment	Taken to site by Study Team	Provided by Local Site
Dental chair (desirable)		X
Mobile intra-oral scanner	X	
Laptop for use with scanner	X	
Intra-oral scanner disposable sleeves	X	
Intra-oral scanner disinfectant kits	X	
High intensity head torch	X	
Boxes of nitrile gloves powder free (100pcs per box)	X	
20x mouth mirrors	X	

20x single ended straight dental probes for caries exam	X	
20x WHO probes for CPITN exam	X	
20x tweezers	X	
Cotton balls or rolls	X	
Sterile packaging in pouches for transporting the dental equipment	X	
Storage box for transportation of equipment	X	

- A. A digital impression for dental arch alignment will be made using the digital intraoral scanner which will be used to take occlusal, buccal, lingual, approximal and full jaw scans. The scanner will be used, and cleaned, and disinfected, in accordance with the guidance provided by the manufacturer (Dentsply Primescan Connect Operating Instructions, available from <https://www.dentsplysirona.com/en-gb/discover/discover-by-brand/primescan.html>). The digital scans will be captured on a study laptop used specifically for the collection of intraoral scans. On return to the University of Bristol, the scans will be transferred to the study data folder on RDSF. The scans will be analysed using the Modified Huddart-Bodenham Index and Peer Assessment Rating (PAR). Software will be employed to carry out this analysis with manual analysis as an alternative and for reliability checking^{xxxiv}.
- B. Dental health will be measured using the standard protocol for measuring of dental caries of DMFT^{xxxv} - the sum of the number of Decayed, Missing, and Filled Teeth in the permanent teeth. A further calculation of DFT/T (decayed and filled teeth divided by the total number of teeth) will be calculated to derive a score which will assess dental health based on decay, given that many teeth are missing for reasons other than decay in individuals born with cleft lip and/or palate. These scores will be recorded on the Case Report Form.
- C. Periodontal health will be assessed using 2 measures:
- Community Periodontal Index for Treatment Needs (CPITN)^{xxxvi,xxxvii,xxxviii}: The World Health Organisation's (WHO) Basic Periodontal Examination (BPE) probe which has a 'ball end' 0.5mm in diameter and a black band from 3.5mm to 5.5mm will be used to perform the Basic Periodontal Exam (BPE) to drive the CPITN score. A total score will be derived from the 6 sub scores of the CPITN. This periodontal health score will be recorded on the Case Report Form.
 - Simplified Oral Hygiene Index (OHI-S)^{xxxix}: OHI-S is a simplified version of the Oral Hygiene Index that measures 6 surfaces of 6 selected teeth. The OHI-S has 2 components, the Debris Index and the Calculus Index. The labial surfaces of upper right and lower left central incisors are scored. In the absence of central incisors on one side, the opposite site incisors are scored. The buccal surfaces of the upper first molars and lingual surfaces of lower first molars are scored. In the absence of first molars, the next available distal tooth (second or third molars) is scored. These scores will be recorded on the Case Report Form to derive the overall OHI-S score.

Station 5: Self-Report Questionnaires Part 2

Station 5 will be similar to Station 1. Participants will be provided with part 2 of the self-report questionnaire to complete on an electronic device (tablet). It is anticipated that completion of the Self-Report Questionnaire part 2 will take approximately 20 minutes.

The questionnaire comprises the following:

A. *Oral Health Impact Profile (OHIP-14)*^{xi}

This 14-item questionnaire will be used to measure participants' satisfaction with their teeth, mouth or dentures in their daily life.

B. *Dental access questions*

These questions ask about the participants' access to dental care and will provide data which may be important in explaining the relationship between exposures and outcomes. These questions have been developed by cleft specialist dentists.

C. *Orthodontics questions*

These questions will also be important in explaining outcomes of orthodontic treatment and the degree to which outcomes may have changed since the end of treatment. These questions have been developed by cleft specialist orthodontists.

D. *Work Productivity and Activity Impairment (WPAI) Questionnaire: General Health*^{xli}

This six-item questionnaire will be used to measure the effect of participants' health problems on their ability to work and perform regular activities.

E. *Modular Resource Use Measure (ModRUM)*

These questions will ask about participants' use of health care resources over the previous six months to measure variation in the costs of healthcare use in the sample.

F. *Private Healthcare Use*

This section asks participants of any use of private healthcare they may have used because of their cleft in the last 6 months.

G. *Out-of-pocket Expenses*

This section asks participants of any out-of-pocket expenses they may have had related to their cleft healthcare and post-secondary education (if applicable) in the last 6 months.

H. *Harter self-perception profiles*^{xlii}

These eight statements ask participants about their sociability and relationships.

I. *Revised Life Orientation Test (LOT-R)*^{xliii,xliv,xlv}

These ten statements provide information on participants' outlook and world view, which could impact on their satisfaction with outcomes.

J. *Patient Reported Outcome Measurement Information System (PROMIS)*^{xlvi}

The PROMIS Scale - Global Health is a standardized psychometric instrument containing 10 questions will be used to measures the participants' global health related quality of life. It supersedes the SF36, but we have retained the five emotional role questions from the SF36 in part 1 of the questionnaire given their importance as the primary outcome measure.

K. Closing questions

At the end of the self-report questionnaire, we will include an optional section which will focus on how having a cleft may have had a positive impact on participants. This section will comprise of a series of statements that the participant can opt to complete one or more of. The statements will include one or more of the following sentences for participants to complete:

- Advice I would give my younger self...
- I'm proud of myself because...
- Something I want people to know about me is...

This section has been added following recommendations from our stakeholders and PPI group. The PPI group have suggested these options as they are more neutral or positively focused than some of the other questionnaire sections and hopefully provide a positive way to end the research clinic for participants.

The responses provided in this section will be collated and analysed using thematic analysis methods and will be reported as a distinct set of data rather than being linked to the other data from participants. This analysis will be published in both peer-reviewed journals and in lay summary form on websites and other public facing domains. The analysis of these data will hopefully provide hope and encouragement to families and younger people who are at earlier stages in the journey towards end of routine care.

Once part 2 of the self-report questionnaire is completed, the participant will be invited to contribute to the Cleft@18-23 'word wall' – a poster board where participants can write their words to complete the sentence, 'I am proud of myself because...'. This is optional and does not form part of the research data but has been added following input from our PPI partners and discussion regarding ending the research clinic on something positive.

A summary of all the data collected in the Cleft@18-23 Research Clinics is provided in Table 6.

Table 6. Summary of data to be collected in the Cleft@18-23 Research Clinics

Research clinic station	Onsite activity	Remote activity (in Bristol)	Type of variable	Specific outcome domain
1. Self-report Questionnaire Part 1	Demographic including EDI characteristics	N/A	Exposure/confounder/ covariate and for sample stratification	
	Computerised adaptive testing (CAT) of CLEFT-Q	N/A	Outcome – self-report	Satisfaction with appearance and function
	SF (Short Form)- 36 (also known as MHI-5) (<i>primary outcome variable</i>)	N/A	Outcome – self-report (psychosocial)	Health related quality of life (emotional)
	Patient Health Questionnaire (PHQ-8)	N/A	Outcome – self-report (psychosocial)	Depression
	Generalised Anxiety Disorder (GAD-7)	N/A	Outcome – self-report (psychosocial)	Anxiety
	Self-report - Health Literacy Questionnaire (HLS-Q12)	N/A	Exposure/confounder/ covariate	
	Connor-Davidson Resilience Scale (CD-RISC-10)	N/A	Outcome – self-report (Psychosocial)	Resilience
2. Medical Photography	Standardised 2D photographs following IMI cleft audit guidelines	Asher McDade scoring/Dental Aesthetic Index	Outcome – clinical	Nasolabial appearance/ teeth appearance
	3D images	Automatic measurement from camera software	Outcome - clinical	Facial shape
3. Hearing and speech assessment	Pure tone audiometry (Hear X Self-Administered hearing assessment)	N/A	Outcome – clinical	Hearing
	Audio-visual recording of a speech sample	CAPS-A analysis	Outcome – clinical	Speech

4. Dental examination	Intraoral scans	Modified Huddart Bodenham Index/PAR	Outcome – clinical	Dental arch alignment
	DFT/T	N/A	Outcome – clinical	Oral health – dental
	CPITN and MPS	N/A	Outcome – clinical	Oral health - periodontal
5. Self-report Questionnaire Part 2	OHIP (Oral Health Impact Profile)-14	N/A	Outcome – self-report	Satisfaction with oral health
	Dental Access questions	N/A	Confounder/Covariate	Access to treatment
	Orthodontic questions	N/A	Confounder/Covariate	Orthodontic treatment
	Work Productivity & Activity Impairment (WPAI)	N/A	Outcome – self-report	Productivity loss
	Modular Resource Use Measure (ModRUM)	N/A	Outcome – self-report	Resource use
	Private Healthcare Use	N/A	Outcome – self-report	Use of private healthcare
	Out-of-pocket Expenses	N/A	Outcome – self-report	Out-of-pocket expenses
	Harter self-perception profile	N/A	Outcome – self-report (psychosocial)	Social functioning
	Life Orientation Test (LOT-R)	N/A	Confounder/covariate	World view
	Patient Reported Outcome Measurement Information System (PROMIS)	N/A	Outcome – self-report	Global health related quality of life
	Positive statements to complete	Thematic analysis	Qualitative data	

The research clinic ends once part 2 of the Self-report Questionnaire has been completed and the participant will be given a £50 voucher, as a thank you for their time, from the study team. At this point, the participant will also be offered the opportunity to meet with a clinical psychologist or

member of the clinical team if they would like to do so. No research data will be collected during this contact. This facility has been costed into the grant and will be made available in recognition that the clinic may raise issues for the participant which they would benefit from talking through with someone who is clinically trained. See Section 18.2 below for more details. No further follow up is required.

17.4.2 Qualitative assessments

Work packages 2-4 are qualitative aspects of this research programme. Protocols and associated documentation will be submitted to REC/HRA as amendments closer to the time of each work package beginning.

17.5 Withdrawal criteria

A participant can withdraw from the study at any time by contacting the study team in Bristol and informing them in writing (by email or postal letter). If they withdraw before attending the research clinic or while attending the research clinic, they can request that all data relating to them be removed if they wish. If they withdraw after they have completed their visit to the research clinic, it will be possible to remove their data from any future analysis but not for analysis which is ongoing or complete. It is necessary for some limited data to remain for audit purposes. This is made clear to the participants in the Patient Information Sheet.

18 ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Research Governance Statement

This study will be conducted in accordance with:

- The principles of Good Clinical Practice, as set out in the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- The UK Policy Framework for Health and Social Care Research.

18.2 Assessment and management of risk

There is a chance that participants may become uncomfortable during the Cleft@18-23 Research Clinic. Every effort will be made to support them, and participants will be asked if they would like someone to accompany them in the clinic stations. There is also the chance that participants may become upset or distressed during the research clinic. For this reason, we have devised a 'distress protocol' with input from psychologists and the PPI group.

The distress protocol outlines clearly the actions to be taken should a participant show signs of becoming upset or distressed. It is intended that the actions outlined in the protocol will enable the participant to recover and, if they would like, to continue with the clinic. The distress protocol details what actions to be taken should a participant not wish to continue, and additional support is required.

As described above, there is also the opportunity for any participant to meet with a clinical psychologist or other clinically trained member of the team for support or to discuss any issues that have been raised for them while attending the clinic.

18.3 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from a REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

All correspondence with the REC will be retained.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

18.4 Regulatory Review & Compliance

The study will be performed subject to favourable opinion/ authorisation/permission or equivalent from all necessary regulatory and other bodies. This includes but is not limited to REC, HRA, NHS Trusts.

Before any site can enrol patients into the study, the Chief Investigator, Principal Investigator or Programme Manager will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

18.5 Amendments

Amendments will be tracked using a version control document.

Substantial amendments require review by NHS REC and will not be implemented until that review is in place and other mechanisms are in place to implement at site.

For any amendment to the study, the Chief Investigator or Programme Manager, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or Programme Manager will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

18.6 End of study

End of study for Cleft@18-23 is defined as the date of end of the grant, which is 31/03/2029.

The Chief Investigator will notify the REC of the end of the study.

At the end of the study, all data will be stored on the University of Bristol Research Data Storage Facility (RDSF).

19 Patient & Public Involvement (PPI)

Focus groups with members of the patient community, specifically 10 young adults aged between 16 and 20, informed the development of the funding application. A PPI group has now been established for the study and this group has informed key elements in the writing of the protocol and development of recruitment resources. We have an ongoing process for recruitment to the PPI group to ensure that we have sufficient PPI representation throughout the study.

PPI has informed:

- The acceptability of the research
- Design of the research

PPI will have an ongoing role in:

- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings

20 PROTOCOL COMPLIANCE

Protocol compliance will be achieved via training all individuals involved with the study for the relevant sections. The study team will all be required to read and adhere to the protocol at all times.

20.1 Protocol Deviations

Should a protocol deviation occur this will be documented and reported to the Chief Investigator and Sponsor immediately.

Protocol deviations will be reported as:

- **Summary of the event:**
[what has happened, how was this identified, steps taken to determine extent of situation (e.g. efforts taken to find consent forms), sites involved in finding]
- **Corrective Action:**
[what action has been taken to correct the situation]
- **Preventative Action:**
[what action will be taken to prevent the situation happening again the future]

These reports will be assessed by the Chief Investigator and Sponsor. Deviations from the protocol which are found to occur more than once will be investigated and further preventative actions will be put in place to prevent repetition of the deviation.

20.2 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

- (a) the safety or physical or mental integrity of the participants of the study; or
- (b) the scientific value of the study

The sponsor will be notified immediately of any case where the above definition applies during the study

21 DATA PROTECTION AND PATIENT CONFIDENTIALITY

Data is held on a combination of restricted access network folders and the University of Bristol (UoB) servers. All the above rely on Windows authentication administered by the UoB IT services and have been approved for storage of this kind of data.

Data generated by the Cleft@18-23 study will be maintained on secure servers at the University of Bristol which are backed up on a regular basis. The University infrastructure consists of real time mirroring of data across two geographically separate data centers as well as off-site tape backups on a nightly basis.

Primary source material (E.g. questionnaires, case report forms and consent forms) will be preserved as electronic (scanned) and hard (paper) copies where practicable. Paper copies of consent forms, case report forms and questionnaires will be stored in locked offices only accessible to the Cleft@18-23 team. Data sources and consent forms will be stored separately from each other in locked offices.

Where data are disposed of this will be carried out securely and in line with University IT Information security policies.

Each participant will be given a study ID number that is linked to their personal information and research data. Only the study team will be able to link the ID number to the participant. Research data items will be stored separately from administrative data and will be accessible only to specified members of the team. Only those members of the study team who require access will have ability to access the data.

All study staff complete the University's mandatory Information Governance training.

At the end of the study, all data will be stored on the University of Bristol Research Data Storage Facility. It will be stored indefinitely and made available to external researchers following the process which will be detailed in a data access policy. This will include the need for submission of a proposal for use of the data, ethical approval for the analysis planned and approval from the data custodians.

We will follow the standards and policies set out by University of Bristol. Further information on data security can be found here: <http://www.bristol.ac.uk/infosec/policies/>.

22 DATA MANAGEMENT

22.1 Data collection tools And Source Document Identification

22.1.1 Source Data

All paper documentation that is collected, which includes consent form and case report forms from the research clinic as well as paper analysis of the speech recordings, will be stored in the lockable rooms at the study base at the University of Bristol. Scanned copies of these documents will be stored electronically in the study data folders on University of Bristol servers.

All electronic data collected in the clinics, which includes the initial contact form and the self-report questionnaire part 1 and 2 completed at the research clinics, will be exported and saved to the study data folders on the University of Bristol servers.

All image data collected at the clinics, which includes 2D and 3D images from the medical photographer station and the video recorded in the hearing and speech station, will be initially stored on SD cards and then transferred to the study data folders on University of Bristol servers. The audio recording collected in the hearing and speech station will similarly be transferred from the audio recording device to the study data folders on the University of Bristol servers. The intraoral scans will be automatically saved to the high spec laptop which is included in the intraoral scanning system. The files from the intraoral scans will also be uploaded to the study data folders on the University of Bristol servers. All electronic data files will be labelled with the participant's study 5-digit ID code together with a description of the specific data type. A SOP will be developed to ensure consistency in this labelling.

22.1.2 Source Documents

Where applicable a random sample of at least 10% of CRFs will be checked, by the study Research Team, against entries within the database and with the source data for quality purposes. The percentage checked will be increased if a significant error rate is found. In addition, the first set of recruitment data collected from a new site will be scrutinized.

22.1.3 Case report forms (CRF)

The Case Report Form will be used to track the progress of the participant around the stations of the clinic and as a checklist for completion of each element within each station.

22.1.4 CRFs as Source Documents

The CRF will contain data collected during the research clinic and therefore will be one of the source documents.

22.1.5 Linking to Other Records

Consent will be requested from participants for the study team to access and link to health, education and CRANE (Cleft Registry and Audit Network) data. Health data from NHS England/NHS Wales/NHS Scotland or the Health and Social Care Board (Northern Ireland), will be requested to provide information on surgical interventions received by the participant, this will assist in explaining variation in outcomes.

Education data from the Department for Education (England), the Department for Education and Skills (Wales), the Scottish Government Learning Directorate (Scotland) and the Department of Education and the Education Authority (Northern Ireland) as well as School education records held by the Office for National Statistics (ONS) in England and Wales, will be used to provide information on education outcomes.

CRANE data will provide information on 5-year-old outcomes for some participants in the sample, permitting an analysis of the degree to which outcomes at age 5-years-old are predictors for outcomes at the end of routine care.

We will also ask for consent to access specific data from cleft records held at regional cleft centres, specifically the information on the participants' cleft subtype, syndromic status, additional diagnoses, and number and type of surgeries. These data will be important for stratifying the sample and also for use as confounder and covariate variables in statistical analyses.

22.2 Data handling and record keeping

The database will be designed so as to protect participant information in line with the General Data Protection Regulation (GDPR). Study staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at the study centres (as relevant) in line with the Ethics approval. All documents will be stored securely and only accessible by study staff and authorised personnel. Data will be collected and retained in accordance with the General Data Protection Regulation.

22.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections- in line with participant consent.

22.4 Access to the final study dataset

It is important to maximise the use of all data collected in research activity. For this reason, we will ask participants for consent to share their data with other researchers who have submitted an ethically approved proposal describing what data they wish to access and how they wish to use it. A system for processing applications to share data will be developed during the course of the study and submitted to the REC for review.

23 STATISTICS AND DATA ANALYSIS

23.1 Sample size calculation

A sample of 600 would allow a mean score of 86.4 to be estimated (95% confidence interval: 84.2-88.6, mean and standard deviation based on Foo et al^{xlvii} for the primary outcome measure, the limitations in usual role activities because of emotional problems in SF-36. With just over 1000 babies born each year with CL/P, the total population available to recruit from over a two-year period is approximately 7000 (1000 individuals born with cleft each year for ages 18,19,20,21,22,23 = 6000 individuals + a second year of recruitment will include young adults who turn 18 in the first year of recruitment). The recruitment rate for a comparable study run by the same team and involving younger children was 75%^{xvi} therefore recruiting 600 is achievable. Nevertheless, we propose to over-recruit by 40 (total sample size 640) as contingency for missing data.

Our work with young people to date suggests that they would be willing to attend this Research Clinic.

23.2 Planned recruitment rate

To achieve a sample size of 640, we aim to recruit from across the UK's cleft centres. Some serve a larger population than others so it is likely that we may recruit more from some sites than others.

23.3 Statistical analysis plan

Descriptive statistics will be used to summarise the exposures (ethnicity, sex, gender, socio-economic status, health literacy and geographical location) using frequencies and percentages. For the outcomes (see table 6), central tendency and variation will be summarised by means and standard deviations or medians and inter-quartile ranges, as appropriate.

Regression models will be used to assess associations between the exposures and the primary outcome. Secondary analysis will be based on regression models for each of the other outcomes separately. Linear, logistic, ordinal logistic or Poisson regression will be used to model associations for continuous, binary, ordinal or discrete outcomes respectively; continuous outcomes will be transformed before analysis if model residuals are skewed.

Directed acyclic graphs (DAGs) will be used to conceptualise associations between variables to enable an appropriate set of confounders to be selected for modelling each exposure-outcome association; age and the other exposures will be considered as potential confounders. All models will be fitted before and after adjustment for appropriate confounders.

Potential cleft centre-level variation for each outcome will be identified through estimation of variance partition coefficients from multi-level models with centre treated as a random effect, adjusting for appropriate (e.g. age and sex) fixed effects. Any outcomes displaying centre-level variation will be modelled using multi-level rather than single-level models.

Potential effect modification through cleft subtype and/or syndromic status will be tested through inclusion of interaction terms in models; if the exposure-outcome association differs according to the categories of cleft subtype/syndromic status, category-specific regression estimates will be presented.

23.4 Economic evaluation

Health economic data will be collected through the Self-report questionnaire part 2 and will be analysed to determine variation in resource use within the sample.

24 SAFETY REPORTING

Adverse events will only be recorded where directly related to study procedures. All adverse events will be recorded and reported in accordance with UHBW's Research Safety Reporting SOP.

25 QUALITY ASSURANCE, RISK ASSESSMENT AND MONITORING

25.1 Monitoring, audit and inspection

The study will be monitored in accordance with UHBW's Monitoring SOP. All study related documents will be made available on request for monitoring and audit by UHBW, the relevant Research Ethics Committee and for any other regulatory authorities.

25.2 Peer review

The plans described in this protocol were reviewed as part of the successful funding application to the NIHR Programme Grants for Applied Research scheme and has also been reviewed by the sponsor.

26 INSURANCE AND INDEMNITY

This is an NHS-sponsored research study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim. The University of Bristol holds Professional Negligence insurance to cover the legal liability of the University, for harm to participants arising from the design of the research, where the research protocol was designed by the University.

27 FINANCIAL OTHER COMPETING INTERESTS, FINANCE AND CONTRACTUAL ARRANGEMENTS INCLUDING EQUIPMENT SUPPLY AND INTELLECTUAL PROPERTY

The study is funded by an NIHR Programme Grant for Applied Research (NIHR205006).

The Cleft@18-23 study team and all PIs must disclose any ownership interests that may be significantly affected by the study. Competing interests will be reported in all publications and in the final report.

All Background IP and Know How used in connection with the study will remain the property of the Party introducing the same. All Foreground Intellectual Property will be owned by University Hospitals Bristol and Weston NHS Foundation Trust. All Arising Know How will be owned by the party that creates it. Research Data is owned by University Hospitals Bristol and Weston NHS Foundation Trust.

The necessary study insurance is provided by the Sponsor and the University of Bristol. The Participant Information Sheet contains a statement regarding indemnity.

28 PUBLICATION AND DISSEMINATION

28.1 Dissemination policy

Academic outputs

These will include papers published to peer reviewed journals and conference presentations from each work package. The conferences will be ones most frequently attended by the cleft clinical and academic community. In the UK, this is the annual meeting of the Craniofacial Society of Great Britain and Ireland. This will also provide opportunities for us to co-present findings with PPI contributors as well as run workshops to explore the findings with clinical teams. Internationally, we will also submit abstracts for presentation at the International Cleft Congress and the American Cleft Palate Association Conferences which take place annually.

Informing and engaging with stakeholders

CLAPA are our route to the patient community, and they will be our primary partner in the development of public facing outputs. CLAPA have an active local network of employed staff and volunteers. We will work with them to ensure the outputs reach the relevant communities. We will also use the media to engage with the public more generally, including through print and broadcast media. Working with our PPI group is likely to be the best way to tell the story of the work that will have been carried out and achieve reach outside of the cleft community.

While these are the routes we are suggesting, we will work closely with our PPI group and co-applicants to identify additional channels.

29 DOCUMENT STORAGE AND ARCHIVING

Study documents (paper and electronic) will be retained in a secure location during and after the study has finished. All electronic documents, including participant records and other source documents will be retained indefinitely in the University of Bristol's Research Data Storage Facility. Paper documents will be retained indefinitely with UHBW's approved offsite data storage facility.

30 REFERENCES

ⁱ <https://www.crane-database.org.uk/reports/crane-database-2021-annual-report/> Accessed 30/11/22

ⁱⁱ Fitzsimons, K., et al., (2013) Hospital care of children with a cleft in England. *Arch Dis Child*, 98, 970-974.

ⁱⁱⁱ Davies, J., Davidson, E., Southby, L., Harding, S., Wren, Y. (2022). Identifying preferred clinical and patient reported outcomes for young people aged 15-20 years born with cleft lip and palate. Presentation at International Cleft Congress, Edinburgh, July 2022. (Paper in preparation)

^{iv} Fitzsimons, K., et al., (2013) Hospital care of children with a cleft in England. *Arch Dis Child*, 98, 970-974.

^v Hunt, O. et al. (2005). The psychosocial effects of cleft lip and palate: a systematic review. *Eur J Orthod*, 27(3), 274-285.

^{vi} Stock, N. M., & Feragen, K. B. (2016). Psychological adjustment to cleft lip and/or palate: a narrative review of the literature. *Psychology & Health*, 31(7), 777-813.

^{vii} Acum, M., et al. (2020). The Psychosocial Patient-Reported Outcomes of End of Pathway Cleft Surgery: A Systematic Review. *Cleft Palate Craniofac J*, 57(8), 990–1007.

^{viii} De Queiroz Herkrath, A. P. C. et al. (2015). Measurement of health-related and oral health-related quality of life among individuals with nonsyndromic orofacial clefts: a systematic review and meta-analysis. *Cleft Palate Craniofacial J*, 52(2), 157-172.

-
- ^{ix} Gallagher, E. R., & Collett, B. R. (2019). Neurodevelopmental and academic outcomes in children with orofacial clefts: a systematic review. *Pediatrics*, 144(1).
- ^x Ware, J. E. (1993). SF-36 health survey: manual and interpretation guide. Health Institute.
- ^{xi} Elovainio, M., Hakulinen, C., Pulkki-Råback, L., Aalto, A. M., Virtanen, M., Partonen, T., & Suvisaari, J. (2020). General Health Questionnaire (GHQ-12), Beck Depression Inventory (BDI-6), and Mental Health Index (MHI-5): psychometric and predictive properties in a Finnish population-based sample. *Psychiatry research*, 289, 112973.
- ^{xii} Shrestha, A., Hoang, H., Gardner, S., Pradhan, A., & Crocombe, L. (2022). Prevalence of Cleft Lip and Palate in the Developing Countries of Asia and Africa: A Review. *Journal of Nepal Paediatric Society*, 42(2), 1-5.
- ^{xiii} Reekie, T. (2011). The effect of South Asian ethnicity on satisfaction with primary cleft lip and or palate repair. *Journal of plastic, reconstructive & aesthetic surgery*, 64(2), 189-194.
- ^{xiv} <https://arc-em.nihr.ac.uk/arc-store-resources/equality-impact-assessment-eqia-toolkit>
- ^{xv} NIHR (2020) Improving inclusion of under-served groups in clinical research: Guidance from the NIHR-INCLUDE project. UK: NIHR. Available at: www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-from-include-project/25435 (accessed 15/07/2024)
- ^{xvi} Persson, M., Sandy, J. R., Waylen, A., Wills, A. K., Al-Ghatam, R., Ireland, A. J., ... & Ness, A. R. (2015). A cross-sectional survey of 5-year-old children with non-syndromic unilateral cleft lip and palate: the Cleft Care UK study. Part 1: background and methodology. *Orthodontics & craniofacial research*, 18, 1-13.
- ^{xvii} Harrison, C., Apon, I., Ardouin, K., Sidey-Gibbons, C., Klassen, A., Cano, S., ... & Rodrigues, J. (2023). The development, deployment, and evaluation of the CLEFT-Q Computerized Adaptive Test: a multimethods approach contributing to personalized, person-centered health assessments in plastic surgery. *Journal of medical Internet research*, 25, e41870
- ^{xviii} Ware, J. E., Kosinski, M., & Keller, S. (2001). SF-36 physical and mental health summary scales. *A user's manual*, 1994.
- ^{xix} Kroenke, K., Strine, T. W., Spitzer, R. L., Williams, J. B., Berry, J. T., & Mokdad, A. H. (2009). The PHQ-8 as a measure of current depression in the general population. *Journal of affective disorders*, 114(1-3), 163-173.
- ^{xx} Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine*, 166(10), 1092-1097.
- ^{xxi} Pelikan, J. M., Link, T., Straßmayr, C., Waldherr, K., Alferts, T., Bøggild, H., ... & Vrdelja, M. (2022). Measuring comprehensive, general health literacy in the general adult population: the development

and validation of the HLS19-Q12 instrument in seventeen countries. *International Journal of Environmental Research and Public Health*, 19(21), 14129.

^{xxii} Connor, K. M., & Davidson, J. R. (2003). Connor–Davidson Resilience Scale. *Confirmatory Factor Analysis of the Connor-Davidson Resilience Scale*.

^{xxiii} Jones, M. & Volcano, J (2021). IMI National Guidelines: Cleft Lip and Palate Audit Review. Version 2. Available from [2018 Sept IMINatGuidelines CleftLipPalate V2-compressed.pdf](#)

^{xxiv} Asher-McDade, C., Roberts, C., Shaw, W. C., & Gallager, C. (1991). Development of a method for rating nasolabial appearance in patients with clefts of the lip and palate. *The Cleft Palate-Craniofacial Journal*, 28(4), 385-391.

^{xxv} Jenny, J., & Cons, N. C. (1996). Establishing malocclusion severity levels on the Dental Aesthetic Index (DAI) scale. *Australian dental journal*, 41(1), 43-46.

^{xxvi} Louw C, Swanepoel W, Eikelboom RH, Myburgh HC. Smartphone-Based Hearing Screening at Primary Health Care Clinics. *Ear Hear*. 2017 Mar/Apr;38(2):e93-e100. doi: 10.1097/AUD.0000000000000378. PMID: 27764002.

^{xxvii} Shinn JR, Zuniga MG, Macharia I, Reppart J, Netteville JL, Jayawardena ADL. Community health workers obtain similar results using cell-phone based hearing screening tools compared to otolaryngologists in low resourced settings. *Int J Pediatr Otorhinolaryngol*. 2019 Dec;127:109670. doi: 10.1016/j.ijporl.2019.109670. Epub 2019 Sep 5. PMID: 31518844.

^{xxviii} Thompson G, Abdelhamid A, Khudan A, Dobbs S, Suleman MT, Salem OM, Khwaja S. The role of a mobile hearing application in secondary care ENT (HAppENT). *J Laryngol Otol*. 2024 Mar;138(3):289-296. doi: 10.1017/S002221512300138X. Epub 2023 Aug 17. PMID: 38223940.

^{xxix} Sandström J, Swanepoel D, Laurent C, Umefjord G, Lundberg T. Accuracy and Reliability of Smartphone Self-Test Audiometry in Community Clinics in Low Income Settings: A Comparative Study. *Ann Otol Rhinol Laryngol*. 2020 Jun;129(6):578-584. doi: 10.1177/0003489420902162. Epub 2020 Jan 22. PMID: 31965808.

^{xxx} Sell, D., Harding, A. & Grunwell, P. (1998) *GOS.SP.ASS'98 An assessment for speech disorders associated with cleft palate and/or velopharyngeal dysfunction International Journal of Language*.

^{xxxi} John, A., Sell, D., Sweeney, T., Harding-Bell, A., & Williams, A. (2006). The cleft audit protocol for speech—augmented: A validated and reliable measure for auditing cleft speech. *The Cleft palate-craniofacial journal*, 43(3), 272-288.

Sell, D., John, A., Harding-Bell, A., Sweeney, T., Hegarty, F., & Freeman, J. (2009). Cleft Audit Protocol for Speech (CAPS-A): a comprehensive training package for speech analysis. *International Journal of Language & Communication Disorders*, 44(4), 529–548.
<https://doi.org/10.1080/13682820802196815>

- xxxii Lohmander, A., Hagberg, E., Persson, C., Willadsen, E., Lundeborg, I., Davies, J., ... Nyberg, J. (2017). Validity of auditory perceptual assessment of velopharyngeal function and dysfunction – the VPC-Sum and the VPC-Rate. *Clinical Linguistics & Phonetics*, 31(7–9), 589–597. <https://doi.org/10.1080/02699206.2017.1302510>
- xxxiii Pereira, V. J., Tuomainen, J., Lee, K. Y., Tong, M. C., & Sell, D. A. (2021). A perceptual outcome measure of velopharyngeal function based on the Cleft Audit Protocol for Speech—Augmented (CAPS-A VPC-Sum): Validation through a speech osteotomy study. *International Journal of Language & Communication Disorders*, 56(4), 754–767.
- xxxiv Woodsend, B., Koufoudaki, E., Lin, P., McIntyre, G., El-Angbawi, A., Aziz, A., ... & Mossey, P. A. (2022). Development of intra-oral automated landmark recognition (ALR) for dental and occlusal outcome measurements. *European Journal of Orthodontics*, 44(1), 43–50.
- xxxv Anaise, J.Z. (1984), Measurement of dental caries experience-modification of the DMFT index. *Community Dentistry and Oral Epidemiology*, 12: 43-46. <https://doi.org/10.1111/j.1600-0528.1984.tb01408.x>
- xxxvi Cutress, T. W., Ainamo, J., & Sardo-Infirri, J. (1987). The community periodontal index of treatment needs (CPITN) procedure for population groups and individuals. *International dental journal*, 37(4), 222–233.
- xxxvii Gjermo P. (1994). CPITN as a basic periodontal examination in dental practice. *International dental journal*, 44(5 Suppl 1), 547–552.
- xxxviii Ainamo, J., & Ainamo, A. (1994). Validity and relevance of the criteria of the CPITN. *International dental journal*, 44(5 Suppl 1), 527–532.
- xxxix Greene, J. C., & Vermillion, J. R. (1964). The Simplified Oral Hygiene Index. *Journal Of The American Dental Association* (1939), 68, 7–13. <https://doi.org/10.14219/jada.archive.1964.0034>
- xl Slade GD; Derivation and validation of a short-forthn oral health impact profile. *Comtnunity Dent Oral Epidetnol* 1997; 25; 284-90. © Munksgaard, 1997.
- xli Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics* 1993; 4(5):353-65.
- xlvi Harter, S. (2012). *The construction of the self: Developmental and sociocultural foundations*. Guilford Press.
- xlvi Carver, C. S. (n.d.). Life Orientation Test-Revised (LOT-R). *MIDSS*. Retrieved from <https://www.midss.org/content/life-orientation-test-revised-lot-r>
- xlv Carver, C. S., & Scheier, M. F. (2014). Dispositional optimism. *Trends in Cognitive Sciences*, 18(6), 293–299.

^{xlv} Carver, C. S., Scheier, M. F., & Segerstrom, S. C. (2010). Optimism. *Clinical Psychology Review*, 30(7), 879-889

^{xlvi} Ranganathan, K., Shapiro, D., Carlozzi, N. E., Baker, M., Vercler, C. J., Kasten, S. J., Warschausky, S. A., Buchman, S. R., & Waljee, J. F. (2016). The Feasibility and Validity of PROMIS: A Novel Measure of Quality of Life among Children with Cleft Lip and Palate. *Plastic and reconstructive surgery*, 138(4), 675e–681e. <https://doi.org/10.1097/PRS.0000000000002541>

^{xlvi} Foo, P., Sampson, W., Roberts, R., Jamieson, L., & David, D. (2012). General health-related quality of life and oral health impact among Australians with cleft compared with population norms; age and gender differences. *The Cleft palate-craniofacial journal*, 49(4), 406-413.