Study Title: Quality of life after open extremity trauma (QUINTET): a prospective, multi-centre, international study.

Internal Reference Number / Short title: QUINTET study

Ethics Ref: Submitted for REC review

IRAS Project ID: Submitted for IRAS review

Date and Version No: 10/11/2022 version 1.2

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Investigators:	Professor Jagdeep Nanchahal. Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford
Investigators:	Mr Juan Berner, DPhil Student in Evidence-Based Healthcare. Department of Continuing Education, University of Oxford
Investigators:	Mr James Chan, Consultant Plastic Surgeon. Buckingham Healthcare NHS Trust
Sponsor:	*University of Oxford,* *Clinical Trials and Research Governance (CTRG),* *Joint Research Office, 1st floor, Boundary Brook House Churchill Drive, Headington, OX3 7GB.*
Funder:	AO UK & Ireland Major Research Grant
Chief Investigator Signature:	

The investigators declare no conflicts of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY CONTACTS

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QUINTET Core Study Group	Associate Professor Abhilash Jain / abhilash.jain@nhs.net Professor Jagdeep Nanchahal / jagdeep.nanchahal@kennedy.ox.ac.uk Mr Juan Berner / juan.berner@kellogg.ox.ac.uk Mr James K-K Chan / james.chan@kennedy.ox.ac.uk

2. LAY SUMMARY

Open lower limb fractures are life changing events. The management of these patients is complex and best accomplished by multidisciplinary teams. It takes a long time for patients to rehabilitate, and many have permanent loss of function. According to the World Health Organisation, trauma remains relatively neglected in developing countries. We have studied the inequalities of access to treatment from a global perspective by assembling an international collaborative network on lower limb reconstruction (INTELLECT), including hospitals in 16 countries ranging from high to low income. We now plan to take advantage of this network to prospectively study the impact of open lower extremity fracture on quality of life as these data have not been previously described in patients from medium and low-income countries. Participants will be asked to complete validated quality of life questionnaires. This will be the first step to design interventions to help trauma patients across different countries with varying income and healthcare systems from a mental health perspective.

3. SYNOPSIS

Study Title	**Quality of life after open extremity trauma (QUINTET): a prospective, multi-centre, international study.**		
Internal ref. no. / short title	QUINTET Study		
Study registration	ISRCTN reference: 31179727		
Sponsor	*University of Oxford,* *Clinical Trials and Research Governance (CTRG),* *Joint Research Office, 1st floor, Boundary Brook House Churchill Drive, Headington, OX3 7GB.* Email: ctrg@admin.ox.ac.uk		
Funder	AO UK & Ireland Contact person: Val Chip Chase / Email: aouki1@btconnect.com		
Study Design	Observational, longitudinal, prospective		
Study Participants	Patients 18 years of age and above admitted with open lower limb fracture		
Sample Size	Single arm of 215 individuals.		
Planned Study Period	Length of the whole study will span from August 2021 to March 2024. Participants will be involved for a period of 12 months		
Planned Recruitment period	Recruitment will take place from January 2022 to March 2023. Follow up of last group of patients will be complete by March 2024.		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Characterise quality of life after open lower limb fractures in an international sample	- 5-Dimension EuroQol (EQ-5D-3L) - Short Form 12 (SF-12)	- Acute admission - 3 months - 12 months
Secondary	Timeline of treatment of patients with these injuries and encountered complications (observational data)	- Time to debridement - Time to fixation - Time to soft tissue closure - Postoperative superficial infection - Postoperative deep infection - Postoperative non-union - Revision procedures or re-exploration required	Throughout first year post-injury and obtained from patients' clinical records.
Intervention(s)	No interventions will be conducted as part of this study.		
Comparator	There will be no comparators for this study as all patients will have the same exposure: having sustained an open fracture		

4. ABBREVIATIONS

CI	Chief Investigator
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
HRA	Health Research Authority
NHS	National Health Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
WHO	World Health Organisation
INTELLECT	International Lower Limb Collaborative
EQ-5D-3L	EuroQol 5-Dimension 3-Level
SF-12	Short Form 12
QUINTET	Quality of Life after Open Extremity Trauma
RES	Research Ethics Service
SITU	Surgical Interventions Trial Unit

5. BACKGROUND AND RATIONALE

Trauma is a global problem and according to the WHO remains a neglected burden in developing countries[1]. We have undertaken the largest lower limb open fracture study to date. The International Lower Limb Collaborative study (INTELLECT) has gathered data on 2,700 patients from 63 centres in 16 countries, including Australia, Argentina, Chile, Czechia, Egypt, India, Italy, Mexico, the Netherlands, South Korea, Austria, Sudan, Spain, Sweden,Taiwan and the UK. Our interim analysis shows significant inequalities. Countries with no established major trauma pathways for managing these injuries report longer mean time to debridement (72 vs 27 hours), time to definitive fixation (11 vs 6 days), inpatient stay (35 vs 27 days) and higher incidence of deep tissue infection (11.2% vs 7.1%).[2]

To better understand how these disparities could be addressed from a global and sustainable perspective, we believe that it is important to first capture how patients cope after these devastating events[3], which cause not only functional problems, but can also adversely impact mental health[4,5]. This aspect has received considerably less attention than the physical impact of major trauma. A few studies have described patient experience after these injuries, mostly in high-income regions such as the UK[6], the USA[7] and Australia[8]. Results obtained from the WOLFF randomised controlled trial demonstrated that immediately post injury, UK patients sustaining open lower limb fractures scored their self-reported quality of life at levels equivalent to death[9]. Furthermore, a recent systematic review concluded that patient experience, as ascertained by patient reported outcomes, remains unknown in low and middle income countries[10].

Taking advantage of the collaborative network of clinicians we have brought together for INTELLECT, and with the support of the Oxford Surgical Interventions Trial Unit (SITU), we will now conduct a prospective, international, collaborative, multi-centre study on the quality of life after open lower extremity trauma (QUINTET).

6. OBJECTIVES AND OUTCOME MEASURES

Our overall aim is to prospectively characterise the quality of life following open lower limb fractures in an international sample of patients, using the patient-reported 5-Dimension EuroQol (EQ-5D-3L) and Short Form 12 (SF-12), to identify potential risk and protective factors to the initial psychological trauma. This initiative is in line with a recent BAPRAS-supported Delphi study that identified research priorities in our specialty, in which *"Outcome assessments (all areas especially psychosocial)"* was ranked second in importance[11].

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure**
Primary Objective Characterise quality of life after open lower limb fractures in an international sample	- 5-Dimension EuroQol (EQ-5D-3L) [12] - Short Form 12 (SF-12) [13] These are widely accepted quality of life questionnaires.	- Acute admission - 3 months - 12 months
Secondary Objectives Timeline of treatment of patients with these injuries and encountered complications (observational data)	- Time to debridement - Time to fixation - Time to soft tissue closure - Postoperative superficial infection - Postoperative deep infection - Postoperative non-union - Revision procedures or re-exploration required	Throughout the follow-up period (12 months from enrolment, per participant)

7. STUDY DESIGN

Support and ethics approval

We will continue to use the Reconstructive Surgery Trials Network as our collaborative model. Ethics approval will be sought from the University of Oxford Clinical Trials Research & Governance (CTRG), followed by Health Research Authority and Research Ethics Services (RES) before commencement in UK centres. Local approval will also be obtained for international centres before recruiting any participants overseas. The 63 centres that have contributed to INTELLECT will be invited to participate. We have

secured participation of centres in Chile, India, South Africa, Sudan, Spain, the Netherlands, Taiwan and the UK in order to represent high, middle and low-income countries. We are aiming for 10 centres agreeing to participate.

The steering group for QUINTET will submit an IRAS application to facilitate local approval for UK-based NHS centres. Senior clinicians in participating centre overseas will be responsible for obtaining local institutional review board endorsement. The approved study protocol will be submitted for Open Access publication.

Eligibility criteria

Inclusion:

- Patients ≥ 18 years of age with a long bone open lower limb fracture
- Willing and able to provide informed consent

Exclusion:

- Patients whose definitive treatment did not take place in a participating centre.
- Patients not able to commit to follow up
- Patients with more than one long bone open fracture

Consent and data gathering process

Potential participants will be counseled, given supplementary information in print and will have to sign a consent form in a language in which they have adequate fluency prior to enrolment. Collaborators will be responsible for prospectively collecting data characterising the injuries, treatment provided and outcomes. A data gathering pro-forma similar to the one used for INTELLECT will be designed for this purpose, taking into consideration the core outcomes set for open lower limb fractures being developed in Oxford. Clinician and patient-reported data will be collected and stored on a secure, GDPR-compliant, REDCap database hosted at The Kennedy Institute of Rheumatology. Participants will be asked to complete the validated 5Q-5D-5L and (SF-12) patient-reported questionnaires upon admission (documenting pre-injury and post-injury quality of life), at 3 and 12 months post-injury. REDCap compatible tablets, paper forms or electronic submission of data will be used depending on local resources.

Impact

Currently, we **do not know** how patients cope with open lower limb fractures in low and middle income countries from a mental health and quality of life point of view. We **do know** that a collaborative model is able to engage with clinicians overseas, empowering them to audit their results, including sites where this has not been done before. Extrapolating the patient reported outcomes obtained in high-income countries is not only unfair but most likely inaccurate, as patient preferences and concerns may be very different. An international, large-scale study would help describe from a global perspective for the first time what patient experience after their injuries. We consider that identifying potential inequalities along with protective and risk factors is key for the development of succesful interventions that could help patients after these devasting injuries. Following the success of INTELLECT, we see QUINTET as the

next step towards a large-scale, collaborative clinical trials on lower extremity reconstruction again led by UK plastic surgeons.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Patients who are 18 years of age or above, age presenting at a participating centre with a long open lower limb fracture, willing and able to consent for inclusion in the QUINTET study. Patients that require transfer to a non-participating centre for definitive management will be excluded.

8.2. Inclusion Criteria

Patients ≥18 years of age with a long bone open lower limb fracture, willing and able to consent to participate in this study.

8.3. Exclusion Criteria

Patients whose definitive treatment did not take place in the participating centre.

Patients unable to commit to follow up.

Patients with more than one long bone open fracture.

9. PROTOCOL PROCEDURES

9.1. Recruitment

First approach will come from the direct clinical care team of the patient. With information about the study, the patient can then agree to be referred on to an investigator if they so choose. Patients will be provided with a patient information sheet.

9.2. Screening and Eligibility Assessment

Each participant must satisfy all the approved inclusion and exclusion criteria to take part in the study. Collaborators in each participating centre will screen for potential eligible individuals among daily trauma admissions. No re-screening procedures will be undertaken.

9.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any data is retrieved and before he/she completes the standardised quality of life questionnaires.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason

without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be given a minimum of 24 hours to reflect on their participation and will have until the end of their inpatient stay to decide. This will allow adequate time for a minimum of 24 hours to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

9.4. Description of study intervention(s), comparators and study procedures (clinical)

There will be no study interventions of comparators for this project.

9.4.1. Description of study procedure(s)

1. EQ-5D-3L is a validated instrument that measures mobility, self-care, usual activities, pain/discomfort and anxiety depression[12].

2. SF-12 is a quality of life, twelve-item questionnaire which was developed as a shorter version of the original Short Form Health Survey 36[13].

These instruments have been chosen due to their widespread generic use and previous validation in multiple languages for use in similar projects looking at mental health outcomes. Both instruments result in a numeric score that can be recorded to compare repeated measurements.

9.5. Baseline Assessments

A baseline assessment of quality of life will be conducted using the EQ-5D-3L and SF-12 during the patient's emergency admission for treatment of an open lower extremity fracture. This will include completing the questionnaires with the patient's recollection of pre-injury quality of life (T0) and a second measurement with the immediate post-injury status at the moment of enrolment (T1)

9.6. Subsequent Visits

At 3 months (T2) and 12 months (T3) post-injury, patients will be re-assessed using the same set of questionnaires. This will be organised to take place ideally during routine follow up appointments. Investigators will be able to contact non-responsive participants twice to remind them and re-schedule follow-up visits, using the contact details provided upon enrolment. Participants will be given the opportunity to provide telephone responses if not able to attend follow up appointments. This will be decided by the participant and recorded in the consent form. For telephone assessments a script will be provided to ascertain who is answering the questions, using the participant's name and unique study identification number, stored locally and the answers provided. This practice will not vary between recruiting centres, with face-to-face follow-ups being the preferred modality.

9.7. Early Discontinuation/Withdrawal of Participants

During the study a participant may choose to withdraw early from the study at any time. This may happen for several reasons, including but not limited to:

- Inability to comply with study assessments
- Participant decision

Participants may withdraw from active follow-up and further communication but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; e.g., CT-Scans, blood results and disease progression data etc.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely.

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements
- Clinical decision

Patients discontinued from the study will receive standard care after this decision and no further quality of life assessments in regard to the study will be conducted.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

As there are no interventions considered for this study, we are not expecting patients to have to withdraw due to side effects.

9.8. Definition of End of Study

The end of study is the point at which all the study data has been entered and queries resolved.

10. SAFETY REPORTING

No interventions or invasive investigations will be conducted as part of this study; therefore, no serious adverse events are expected to happen. Therefore, we think that safety reporting is not applicable for this study.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

Statistical analysis will be performed in compliance with the STROBE guidelines[14], including descriptive and inferential statistical tests. Injury characteristics, demographic data and treatment modalities

differences will be measured and compared using Fisher's exact test or Mann-Whitney test for independent samples. The recorded quality of life scores obtained along the patients follow up (T0, T1, T2 and T3), and after ascertaining normality of the collected data, will be compared using ANOVA test for related samples. Friedman test will be used instead of ANOVA if there is not a normal distribution of the obtained data. Multivariate analysis will be conducted using multiple linear regression models to measure the impact between clinical variables and quality of life scores at T0, T1, T2 and T3.

11.2. Description of the Statistical Methods

Fisher's exact test is a statistical significance test amenable for small samples used to accept or reject a null hypothesis.

Mann-Whitney U test is a non-parametric test to assess a continuous variable null hypothesis.

Analysis of variance (ANOVA) for related samples is a statistical test to determine if the means obtained from the same population at different stages are equal or not.

Friedman test is a non-parametric statistical used to detect differences in an outcome across multiple test attempts, similarly to the parametric repeated test ANOVA but for data that does not follow normal distribution.

Definitions:
Superficial infection: redness and swelling, with or without discharge, that was treated with antibiotics. If surgery was performed, no evidence of infection was found deep to muscle fascia

Deep infection: infections below muscle fascia, including bone, that require surgical exploration for lavage, removal of metalwork and/or further bone debridement

Non-union: Lack of union requiring unplanned surgical intervention after definitive wound closure or incomplete radiographic healing at 1 year

Amputation: immediate if it is in the first 24 hours, acute if it is performed within 3 months after the injury and late if it is performed after than that.

11.1. Sample Size Determination

Considering the cases collected for the INTELLECT study, it was determined that for the centres agreeing to participate in QUINTET, a total of 541 open fractures were seen on average per year. Assuming that the effect of sustaining an open fracture is unknown from a global perspective ($p = 0.5$), a confidence level of 95% and a precision of 5%, the calculated sample size aiming to measure significant differences in repeated quality of life measures is 215 individuals. We would be able to tolerate an estimated drop out of 20%, resulting in a minimum sample of 175 patients for analysis.

11.2. Analysis populations

Data obtained from all participants enrolled will be analysed. Only data regarding patients that decided to withdraw from the study will be excluded from analysis and erased from the database.

11.3. The Level of Statistical Significance

A two-sided p-value<0.05 will be considered significant when comparing mean scores obtained at T0, T1, T2 and T3.

11.4. Procedure for Accounting for Missing, Unused, and Spurious Data.

We aim to validate 2% of the obtained data by cross examination of records and local research teams. Any spurious, unused or spurious data will be inquired to ascertain reliability.

11.5. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Deviations from the intended analysis plan will be discussed by the core group of investigators and will be included in any resulting reports.

12. DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions as per local protocols. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, regulators and host institution for monitoring and/or audit of the study to ensure compliance with local regulations.

12.3. Data Recording and Record Keeping

All trial data will be entered on a secure and GDPR compliant REDCap database, hosted on servers at the Kennedy Institute of Rheumatology.

The participants will be identified by a unique trial specific number and/or code in the database. The name and any other identifying detail will NOT be included in any trial data electronic file. No study data

other than the consent forms and participant contact details will be stored locally, as per local data security protocols. If paper forms are used for data collection these will be destroyed as soon as the information is uploaded into REDCap. No international identifiable information transfer is planned.

All patient data will be stored in an anonymised manner in the REDCap database for 3 years after completion of the study. After 3 years all participant data will be destroyed. Data will be exported as an encrypted Excel spreadsheet stored at the University of Oxford OneDrive. This will allow processing of the data and later exportation to SPSS software for analysis. The SPSS file will be encrypted and will not contain any identifiable information

No identifiable data will be transferred during the course of the study. Participants will not be given the option to be contacted for future research.

This study is compliant with the University of Oxford's Data Protection Checklist (https://researchsupport.admin.ox.ac.uk/policy/data/checklist) and Practical Considerations (https://researchsupport.admin.ox.ac.uk/policy/data/practical)

13. QUALITY ASSURANCE PROCEDURES

13.1. Risk assessment and study monitoring

A formal risk assessment and study monitoring plan is included as a separate document. Regular core study group meetings will be held to ascertain that the study protocol is being followed.

13.2. Study Committees

A core study group will be formed by Associate Professor Abhilash Jain, Professor Jagdeep Nanchahal, Mr Juan Berner and Mr James Chan. They will oversee the conduction of the study and will deal with any concerns raised by local investigators.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

In the event of the inadvertent receipt of identifiable data or any other potential data incident, we would notify the University of Oxford Data Breach team immediately (data.breach@admin.ox.ac.uk) in order to comply with procedures, set out by the Information Commissioners' Office (ICO).

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval the protocol, informed consent form and participant information sheet will be submitted to appropriate Research Ethics Committees (RECs), the HRA and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committees, HRA, host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.5. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.6. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be anonymised as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and our REDCap electronic database. All documents will be stored securely and only

accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.7. Expenses and Benefits

Participants will not receive any compensation for their participation in this study

17. FINANCE AND INSURANCE

17.1. Funding

The AO United Kingdom & Ireland has provided a competitive grant for £8,500.

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements with third parties and all research sites will be arranged.

18. PUBLICATION POLICY

The results of this study will feed into Mr Juan Berner's DPhil thesis. Results will also be disseminated at plastic and orthopaedic surgery national and international meetings. A manuscript summarising our findings will be submited for Open Access publication, ensuring clinicians in the developing countries will have access to it.

The core group of QUINTET investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by AO UK&I. Authorship will be determined in accordance with the ICMJE guidelines.

An established collaborative model will be used to acknowledge clinicians in participating centres. A minimum of 10 cases with completed 12-month follow-up will be required for each collaborator to be recognised within the QUINTET collaborative.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable

19. ARCHIVING

No study data will be archived following its destruction after 3 years post finalisation of the study. This includes consent forms stored locally. These will be kept securely as per local data storage protocols.

20. REFERENCES

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APPENDIX A: SCHEDULE OF STUDY PROCEDURES

Procedures	**Assessments**			
	Day 0	**During first admission**	**3 months post discharge**	**12 months post discharge**
	Screening	**Baseline**		
Informed consent	X			
Demographics	X			
Case note review	X	X	X	X
Eligibility assessment	X			
5-Dimension EuroQol		X	X	X
Short Form 12		X	X	X

21. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.2	10/11/22	Juan Berner	Recruitment extended until 31st March 2023. Study extended until 31st March 2024.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).