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TITLE:
Study Protocol

Short Title: Clinical usability evaluation of an Adaptive Templates Fitting System for socket design

Full Title: An evaluation of clinical usability-related safety of an Adaptive Templates Fitting System to support prosthetic socket design

in accordance with

BS EN ISO 14155:2020
Clinical investigation of medical devices for human subjects. Good clinical practice

MHRA Guidance on legislation
Clinical investigations of medical devices – compiling a submission to MHRA (v 3.0, May 2021)

REVISION HISTORY			
Rev.	**Date**	**Description of Change**	**Initiator**
XA	17/11/22	Initial Document	JB
XB	01/08/2023	Updated with Radii as sponsor	JB
XC	24/11/2023	Updated study sites	JB
XD	24/01/2024	Updated objectives to specify how safety and performance will be verified	JB
XE	20/02/2024	Updated assessment of patient participant stage 2 sample size	JB
XF	15/03/2024	Updated Group B follow up and recruitment, end of study and Adverse Events process, post-REC review panel	JB

APPROVALS					
Clinical	**Date**	**Regulatory**	**Date**	**Technical**	**Date**
Jennifer Bramley	19th March 2024	Jennifer Bramley	19th March 2024	Joshua Steer	19th March 2024

CONTENTS

1. Summary

Radii Devices Ltd.

And

University of Southampton

And

Ability Matters Group Ltd. (Opcare Ltd)

Short Title: Clinical usability evaluation of an Adaptive Templates Fitting System for socket design

Full Title: An evaluation of clinical usability-related safety of an Adaptive Templates Fitting System to support prosthetic socket design

Chief Investigator: Dr Shigong Guo

Research Team: Pamela Anderson, Jennifer Bramley, Alex Dickinson, Maggie Donovan-Hall, Dominic Hannett, Jack Kitchen, Alex Lewis (Public Contributor), Florence Mbithi, Cheryl Metcalf, Chantel Ostler, Joshua Steer, Peter Worsley

Study Sites: Bristol, Cambridge and Norwich NHS Opcare prosthetics services clinics

Sponsor: Radii Devices Ltd.

Funder: Innovate UK Biomedical Catalyst Grant

IRAS ID: 317901

ERGO NO: 81419

HRA REC REF: 24/LO/0126

NIHR CRN NO: 57956

2. List of abbreviations

AE: Adverse Event

ATFS: Adaptive Templates Fitting System

ERGO: Ethics Research Governance Online

GCP: Good Clinical Practice

GDPR: General Data Protection Regulation

IRAS: Integrated Research Application System

KPI: Key Performance Indicator

MDT: Multidisciplinary Team

MHRA: Medicines and Healthcare products Regulatory Agency

NHS: National Health Service

NIHR: National Institute for Health and Care Research

NRES: National Research Ethics Service

PPE: Personal Protective Equipment

PPIE: Patient and Public Involvement and Engagement

PIS: Participant Information Sheet

REC: Research Ethics Committee

SAE: Serious Adverse Event

3. List of Definitions

Formative usability testing (i.e. Stage 1): according to BS-EN 62366, Iterative testing performed throughout the design and development to explore user interface strengths and weaknesses

Summative usability testing (i.e. Stage 2): according to BS-EN 62366, Final testing stage at the end of design and development to obtain objective evidence to validate user interface

4. Background

A well-fitting and comfortable prosthetic socket is a priority for patients as it is the determining factor in enabling mobility and participation in society[1,2]. It is also a clinical priority, with:

- Increasing demand for prosthetics, with 7,000 amputations/year by NHS England[3], which is growing due to ageing populations, rising diabetes prevalence, and the COVID19 backlog
- NHS cost burden of £60M and growing[2]
- Need to support prosthetists to achieve optimal socket fit, faster, with fewer device rejections

The socket represents the interface between the residual limb and prosthetic componentry. However advanced the componentry, if the socket interface lacks the necessary balance of firm limb-device coupling and comfort, the limb's function will be impaired to the extent that the person may choose not to use the prosthetic limb. This situation is indeed common: rejection rates are 31%[4]. Sockets are designed by a prosthetist, in a process that aims to optimise comfort, stability and mobility for the prosthesis user. In addition, socket fit is dependent on multifactorial patient differences including limb shape, soft tissue stiffness, regional tolerance to load and comorbidities. Sockets are not a 1:1 match of limb shape; instead, the prosthetist makes modifications, or "rectifications," to the baseline limb shape. This is intended to load pressure-tolerant limb regions, and off-load pressure-sensitive sites, to produce a secure and comfortable interface between patient and prosthesis. Rectification is a highly complex, skill- and experience-based process, yet there is little objective guidance or evidence to support prosthetists who require years of training and experience to hone their skills. This complexity leads to multiple iterative re-fittings, with an average of 9 visits to prosthetists in the first postoperative year[5]. Whilst some adjustment and re-fitting is inevitable as the residual limb stabilises in shape and volume, the clinical community is calling for tools to support them in taking a more evidence-based approach to the fitting process, to tackle these service inefficiencies and their socioeconomic impacts.

Since 2014, understanding how best-practice in engineering design can support prosthetic socket fitting has been a key focus of University of Southampton researchers. This research has resulted in the spin out of a company (Radii Devices Ltd.) and the development of technology to meet the patient and clinic need, guided by input from prosthetics service providers including Opcare (Ability Matters Group Ltd.), and patients. This study is assessing the usability of the developed software, Adaptive Templates Fitting System (ATFS), incorporating the technology. These Adaptive Templates use existing socket fitting data, which is analysed to link rectification approaches to particular patient characteristics. The data includes socket designs, limb shapes, and outcome measures from previous socket fittings in the NHS. The ATFS is derived from these datasets in two ways:

1) Extracting features from the complex 3D shapes of the residual limb and prosthetic socket, used for past patients. These may include individual rectifications, and clinically relevant residual limb features, such as the length, and how bulbous or conical their limb is.

2) Making a recommendation to a prosthetist for socket rectifications, using a probabilistic approach which considers the likelihood of particular socket design strategy working for a new patient's characteristics.

Unlocking the potential of data to support fitting will assist more efficient learning and design, potentially leading to:

- Reducing time to fit (fewer iterations, reduced waiting time and, eventually, reduced appointment backlog)
- Reducing rejection rates (improved comfort and functional stability)
- Improving patient outcomes, participation and quality of life (reduced incidence of soft tissue problems, from irritation and sores to major injuries such as pressure ulcers; reduced incidence and progression of comorbidities, including sequelae of immobility, obesity, vascular disease and mental health impacts)

The developed technology, using computational geometry, data science and biomechanical engineering expertise to extract meaningful data about the rectification process has been applied to below-knee prosthetic socket design data provided by Opcare. This data helped form an initial demonstration of the feasibility of linking rectification approaches to particular patient characteristics and objectively analysing personalised design approaches by expert prosthetists[6].

A preceding related study (IRAS ID: 313408, EGRO NO: 76033, REC REF: 22/YH/0215, 01/02/23 – 30/11/23) is being conducted by the same team to compare sockets designed by a clinician to sockets designed by the underlying technology, to explore the feasibility of the proposed new approach. The aims of the study are to understand the strengths and limitations of the technology and fine tune its recommendations. These findings are being used in parallel to develop the ATFS; a full system usable by prosthetists in-clinic to support their socket design process.

The objective of this proposed new study is to evaluate the in-clinic usability of the ATFS, whose development was informed by the preceding feasibility study.

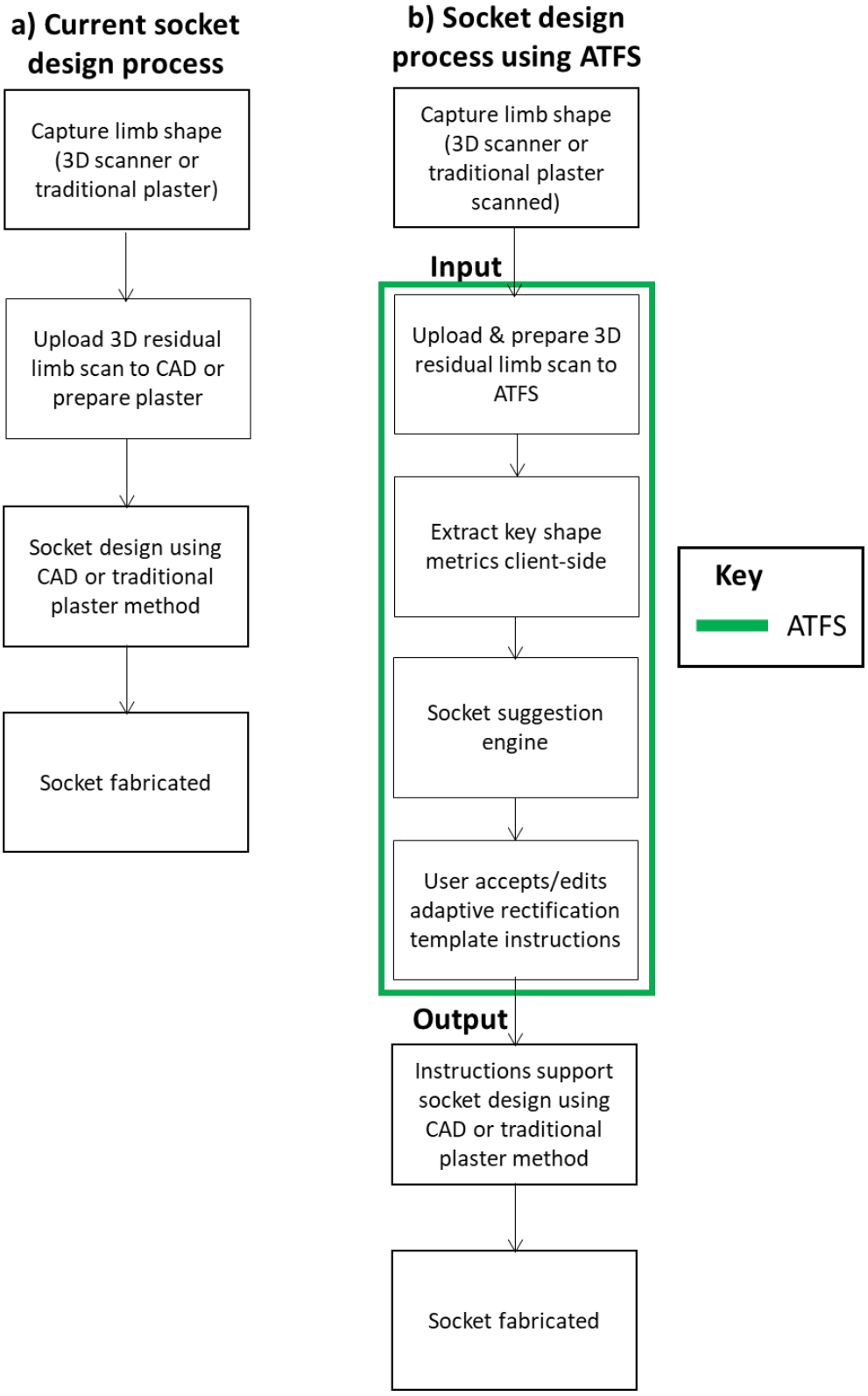
The output of the ATFS is a human-readable instruction set of the recommended rectifications to apply to the residual limb shape to create the socket in their relevant units (mm or %), which takes seconds to produce after upload of the residual limb scan. From here, the prosthetist can accept or edit each recommendation according to their clinical assessment. Therefore, the system is a tool to support the prosthetist based upon historical best-practice.

Following the creation of the instruction set, the socket is created by applying these instructions to modify the captured shape of the residual limb. This process is achieved either digitally with CAD software, which are not considered medical devices in their standalone form, or even manually through modification of a plaster model.

The various use of the ATFS within the socket design process is outlined in the diagram below. The optimal use case, and the one which will be tested in this study, is for the CAD tools to be automatically populated by the template, once approved by the clinician. This case is only possible when using the Radii system due to the integration between the systems.

Alternatively, because the output of the adaptive template is a human-readable instruction set, the user could apply the recommendations through another medium, such as a 3rd party CAD system or even through modification of a plaster model. However, this approach would introduce additional time taken and steps within the process.

The figure below illustrates the separation between CAD tools and the Adaptive Templates Fitting System. This system design is critical to ensure that the clinician is always responsible for the final socket design and can edit the adaptable templates as they see fit according to their expertise.



5. Research objective and tasks

4.1 Research Objective

Following the preceding study (IRAS ID: 313408, EGRO NO: 76033, REC REF: 22/YH/0215, 01/02/23 – 30/11/23), the objective of this study is to evaluate the clinical usability, in terms of safety and performance, of the Adaptive Templates Fitting System that combines Adaptive Templates technology with the experience and expertise of the clinician to provide optimal socket design support. It is important for this clinical investigation to verify the clinical safety and performance of the ATFS to comply with Section 1 of Annex I of the Medical Devices Directive; demonstrating when used for its intended purpose (support of socket design by prosthetists) the safety of patients (those receiving the designed sockets) will not be compromised.

The study will be carried out in two stages contextualised with longitudinal qualitative research, according to study design definitions from BS-EN 62366:

Stage One will explore the strengths and limitations of the in-clinic usability of the ATFS to inform its further development, reducing as far as possible the risk of use error due to user interface, and;
Stage Two will assess the in-clinic usability of the updated ATFS. This clinical investigation will verify the safety and efficiency of its in-clinic use by capturing:

- socket comfort scores of sockets designed using the ATFS to demonstrate non-inferiority compared to the current process (without the support of the ATFS) and socket comfort scores $\geq$ 7, the NHS key performance indicator; and
- time taken for initial rectification and socket design using the ATFS compared to with the current process.

4.2 Study Tasks

Stage One Tasks

- Iterative usability testing of the ATFS for supporting socket design, informing its further development.
- Iterative development of ATFS training materials.
- Design sockets for patients from NHS clinics, provided by Opcare, with the aid of the ATFS.
- Capture outcome measures (e.g., socket comfort scores).
- Explore prosthetists' views and experiences of using the ATFS in their current practice and pathways.
- Evaluate the strengths and weaknesses of the ATFS.
- Integrate findings from qualitative research to further understand experiences from the clinician's perspective to support the development of the ATFS.

Stage Two Tasks

- Usability testing of the final developed ATFS.
- Design sockets for patients from NHS clinics, provided by Opcare, with the aid of the ATFS.
- Capture outcome measures (e.g., socket comfort scores, time taken for initial rectification and socket design using the ATFS for comparison with the standard CAD/CAM socket design process).
- Explore prosthetists' views and experiences of independently using the ATFS in their current practice and pathways.
- Integrate findings from qualitative research to demonstrate safe and efficient clinical usability of the ATFS.

6. Methods and design

6.1 Population

This study will recruit two groups of participants in order to fulfil the research objectives.

The first group will be prosthetists at the three participating centres. This study will explore the experiences of the prosthetists designing sockets with the aid of the ATFS in-clinic, comparing to the standard design workflow used in their prosthetics centres, plus their views on any barriers or facilitators to using the ATFS. These perspectives are vital to ensure that the ATFS is clinically translatable and as useful as possible in supporting the prosthetists' expert socket design process.

The second group will be adults who have undergone a transtibial (i.e. below knee) amputation and are attending the Bristol, Cambridge or Norwich NHS Opcare prosthetic services centres. The study focus will be the design of sockets for below knee amputation, as this has the highest prevalence[7] and as such has been the focus of researchers for CAD/CAM software development[8, 9]. Also, transtibial socket designs are most suited to the ATFS method as they include the most inhomogeneous design features. It is also desirable to work with this patient group first for safety reasons, since individuals with transtibial amputation are less likely to have comorbidities compared to those using transfemoral sockets.

6.1.1 Inclusion and exclusion criteria

Group A – Prosthetists

Inclusion criteria

- Prosthetists working with patients recruited as participants in the study
- Are willing to design a socket using the ATFS

Exclusion criteria

- Not familiar with using CAD software technologies for socket design
- Unwilling to design a socket using the ATFS

Group B – Adults with limb loss

Inclusion criteria

- Over the age of 18
- Have had a transtibial amputation
- Deemed ready to cast for a new prosthesis by the clinical team as per usual care at the prosthetic centre
- Able to understand verbal and written English and give informed consent

Exclusion criteria

- Contraindication to be fitted for a prosthetic socket
- Unwilling for their prosthetist to design their socket using the ATFS
- Unable to answer verbal questions (as per normal fitting appointment) on their socket fitting and comfort

6.2 Population size

Group A – Prosthetists

Prosthetists across the three NHS sites (up to 17 in total) will be recruited in the participating prosthetics centres, allowing several prosthetists' usability experiences to be captured.

For Stage One (the iterative usability testing) BS-EN 62366 suggests that a sample size of 5-8 participants is sufficient. BS EN 62366 illustrates in Annex K that using small sample sizes identifies usability defects and reduces the required clinical resource.

A sample size of 15 participants is suggested according to BS-EN 62366 for the summative usability testing (Stage Two). This sample size gives a probability of capturing at least one occurrence of a usability defect of 91% (IEC/TR 62366-2:2016). A power analysis to determine sample size has not been carried out as BS EN 62366 discourages use of power analysis to determine sample size for usability studies.

A sample size of 17 was determined taking into account BS-EN 62366, the number of prosthetists at each of the NHS sites, allowing for 10% withdrawals, and matching similar published studies exploring clinician perspectives of socket fit[10].

Group B – Adults with limb loss

A sample of convenience of up to 46 adults with transtibial limb loss will be recruited across the three participating prosthetics centres for this study. This sample size was determined by considering the number of usability study iterations that may take place, both patient and prosthetist withdrawals, and demonstration of the clinical usability within Stage Two.

Sample size was determined for the two stages as follows:

Stage One:

For each participating prosthetist in Stage One, one patient participant will be recruited per usability iteration. 5-8 prosthetists will participate in each usability testing iteration. Allowing for withdrawal

and for three iterations, a maximum of 27 patient participants would need to be recruited. Less participants may be recruited if fewer usability iterations are required in Stage One as determined by the technology development process (e.g., feature freeze), and the participating clinicians being comfortable to use the ATFS throughout the full socket design process independently without resorting to their current socket design process (i.e. no further observation or detection of a usability problem).

Stage Two:
A sample size of 19 will be recruited for Stage Two. This sample size was determined using a non-inferiority result for a crossover group trial with normal socket comfort score data. We determined an appropriate sample size of 19 for this group (power: 0.9, significance level: 0.025, Mean Difference: 0, non-inferiority limit: 1.21, population Socket Comfort Score standard deviation: 0.998). This was using the NIHR SampSize web tool with the non-inferiority limit obtained from Hafner et al[11] and population standard deviation obtained from the ATFS training dataset[12] which is an extension to the population presented in Dickinson et al[6]. An addition of 10% was added accepting the uncertainty around the employed data.

6.3 Recruitment

Group A – Prosthetists
Convenience sampling will be used to recruit prosthetists who are interested in taking part at Bristol, Norwich and Cambridge NHS Opcare prosthetic services.

Group B – Adults with limb loss
Convenience sampling will be used to identify participants to take part in the trial. All patients who meet the inclusion criteria and have been referred for limb fitting at one of the participating NHS prosthetics centres, or contact one of the three centres for an assessment appointment within the study period will be invited to take part in the trial. An invitation letter and Participant Information Sheet (PIS) will be sent from participating clinics to potential participants ahead of their assessment appointment to allow them sufficient time to consider taking part in the study prior to the appointment.

6.4 Stage One Procedure – Group A

(Please see prosthetists pathway diagram on Page 13)
Prosthetists will be informed of the study via the study's clinic leads Jack Kitchen – Bristol NHS Opcare prosthetics services clinic, and Pamela Anderson – Cambridge and Norwich NHS Opcare prosthetics services clinics. The study will be discussed at team meetings. A PIS and invitation letter will be circulated to all interested prosthetists via email. Prosthetists who would like to take part will have an opportunity to ask questions and will then be asked to complete a consent form by a member of the Clinical Investigation team. They will be able to consent for both Stages, or just Stage One, or just Stage Two. This is set out clearly in the PIS.

Once recruited, the participating prosthetists will be invited to attend an in-person training session at their clinic carried out by the study researchers to introduce them to the ATFS and guide them through an example case. The objective of the training session will be to ensure they feel comfortable to use the software as an aid in designing a socket for a patient. They will also receive a printed and electronic 'Quick Reference Guide' and be shown the in-software information videos.
Next, the prosthetist will attend the assessment appointment of an eligible patient. During the assessment appointment, after providing the patient with the study invitation letter and the PIS, the prosthetist will capture the patient's residual limb shape with direct a 3D scan of the limb or scanned plaster cast of the limb, and other measurements, as is normal clinical practice. At the end of the assessment appointment, if the patient would like to participate then the attending prosthetist, site Principal Investigator or an attending study researcher will receive their consent.

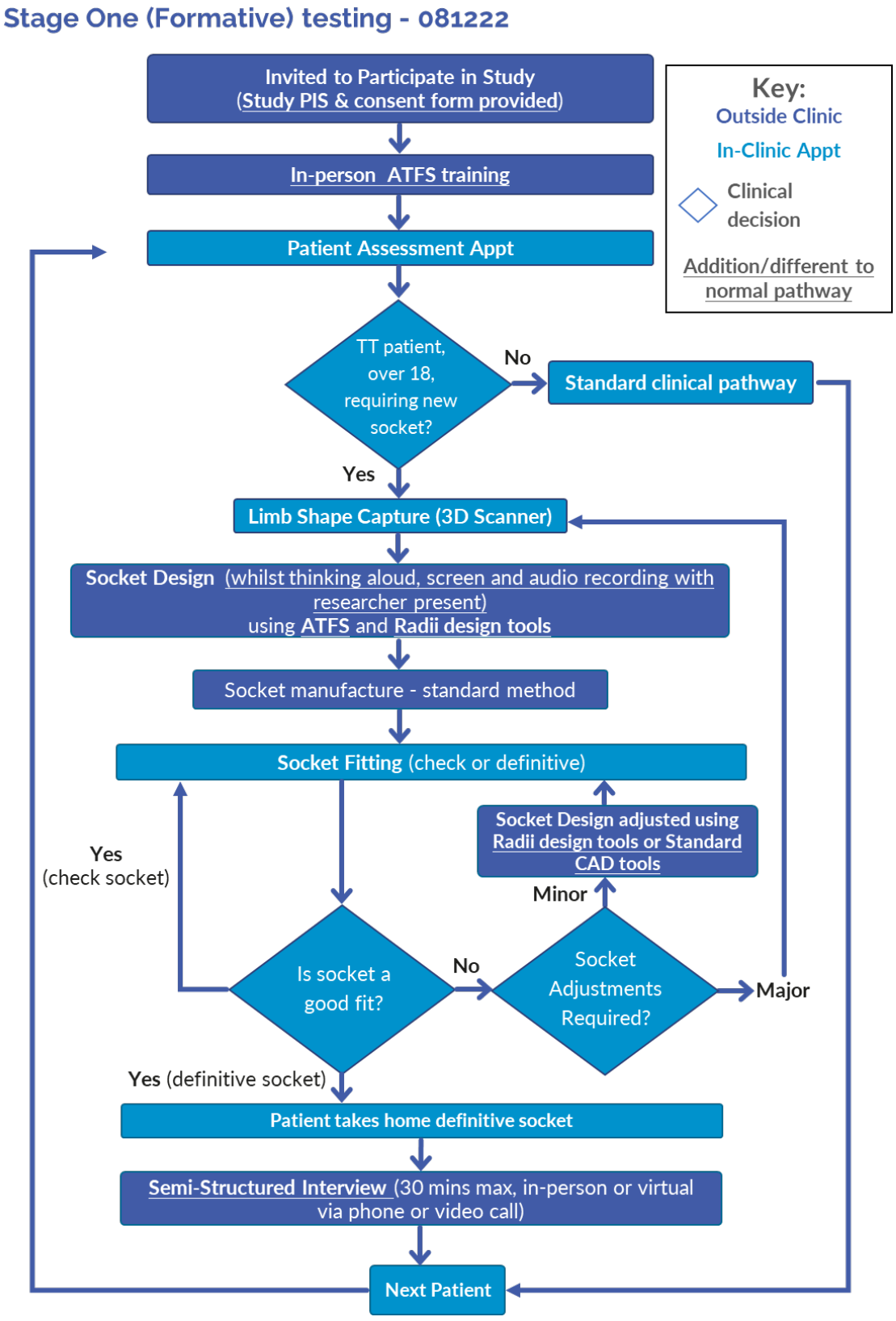
The prosthetist will then access the ATFS, via a web-browser, using login details provided by the study researcher. The prosthetist will upload the limb shape file and use the ATFS to support them designing a socket for their patient. They will be asked to think aloud while using the ATFS. They will be recorded as they use the software, and the study researcher will be available to help where required. Recording will be via screen-capture with audio.
They will then send the designed socket file to their workshop or central fabrication facility for manufacture into a socket as per their clinic's normal process.

As per normal care, once the socket has been made the prosthetist will carry out a fitting appointment for the patient, taking and recording standard outcome measures (e.g. socket comfort score, Key Performance Indicators (KPIs) for their clinic). They will discuss the socket fit with the patient and make minor or major socket adjustments as required, using the ATFS software where digital adjustments are needed, leading to delivering the definitive socket for the patient. The study researcher will be on-call to help where required with use of the ATFS. The socket comfort score will be collected from the prosthetist by a study researcher.
The study researcher will arrange to conduct a 30-minute semi-structured interview with the prosthetist after delivery of the definitive socket to the patient, about their experience creating a socket with the aid of the ATFS. Physical adjustments carried out on the socket during fitting appointments will also be captured during the interview. The prosthetist will have the choice of an in-person, virtual (via MS Teams video call software), or telephone interview. The interview will be arranged flexibly around the prosthetist's schedule.
Training materials on using the ATFS will also be evaluated through the semi-structured interview.

For the iterative development of the software being carried out during this first stage, the prosthetist may be asked to carry out stage one of the study at least once more. Software updates will be pushed throughout Stage One while developing the ATFS and researchers will be present to support ATFS use and provide training as required. The Stage One endpoint and number of usability iterations required in Stage One will be determined by the technology development process (e.g., feature freeze), and the participating clinicians being comfortable to use the ATFS throughout the full socket design process independently without resorting to current socket design process (i.e. no further observation or detection of a usability problem with final ATFS version reached and ready for summative testing).

See Group B – Stage 1 semi-structured interview format in the Appendices of this document in Section 16.1.

Stage One Group A (participating prosthetists) Pathway Diagram:



6.5 Stage Two Procedure – Group A

Stage Two consists of Summative usability testing of the fully developed ATFS. Training will be provided if a participant interested in taking part in only Stage Two did not attend a Stage One training session.

(Please see prosthetists pathway diagram on Page 15)

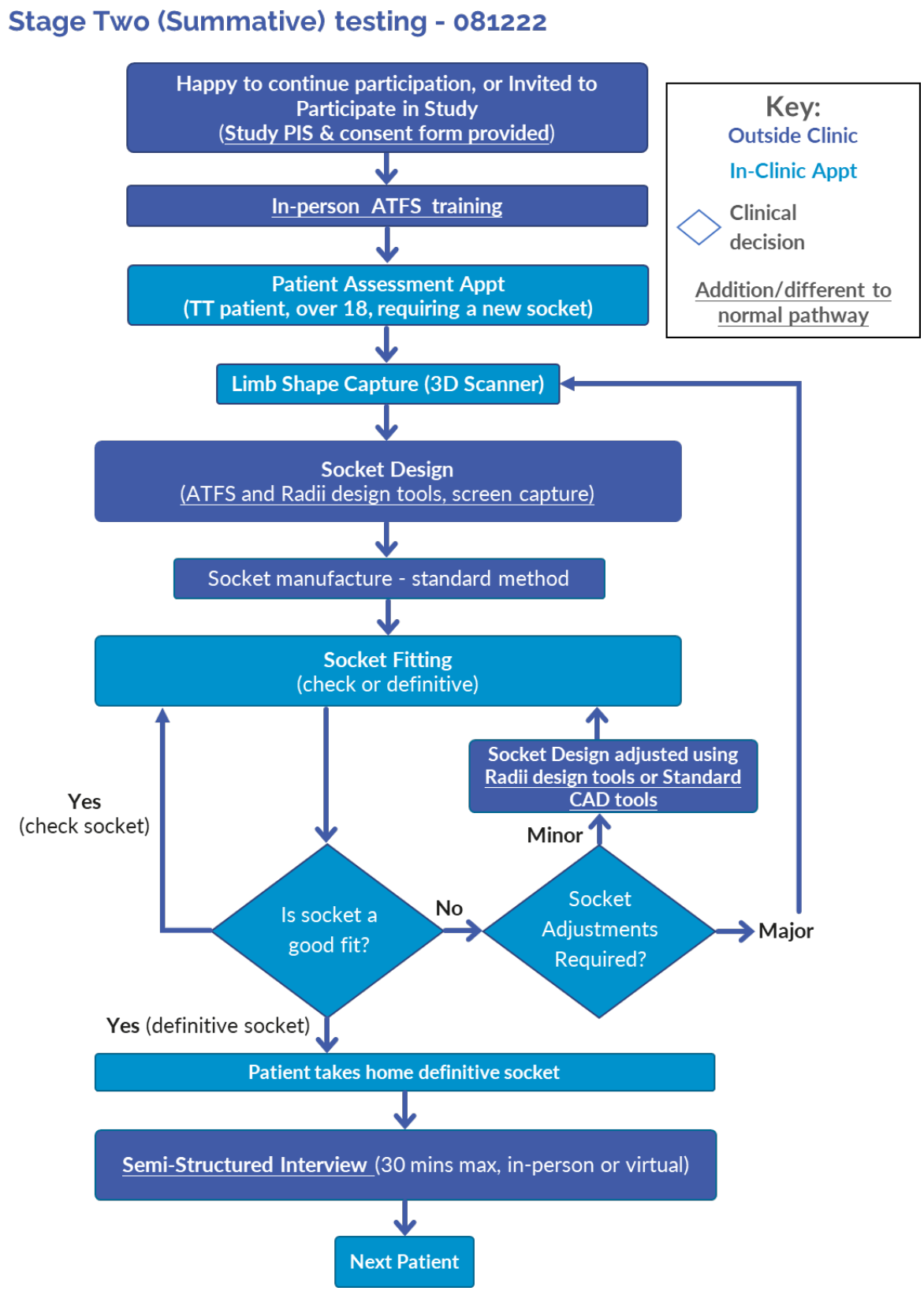
Identical to Stage One except for the following changes:

i. The prosthetist will use the ATFS independently while being recorded but without thinking aloud.
ii. No changes will be made to the ATFS during this stage.
iii. The study researcher will arrange to conduct a 30-minute semi-structured interview with the prosthetist after delivery of the definitive socket to the patient, about their experience independently creating a socket with the aid of the ATFS, plus their views on comparisons against their standard CAD/CAM design workflow.

The interviews will be arranged flexibly around the prosthetist's schedule.

See Group A – Stage 2 semi-structured interview schedule in the Appendices of this document in Section 16.1.

Stage Two Group A (participating prosthetists) Diagram:



6.6 Stage One and Stage Two Procedure – Group B

Group B – Adults with limb loss

Their involvement in this study will form part of a patient's usual care which will be provided according to the NHS Trust's most up-to-date infection prevention and control guidance. When a person with a transtibial amputation who meets the inclusion criteria is referred for prosthetic limb fitting at one of the three participating NHS prosthetics centres, or contacts one of the three centres for an assessment appointment. For both Stages of the study, an invitation letter and Participant Information Sheet (PIS) will be sent from participating clinics to potential participants ahead of their assessment appointment to allow them sufficient time to consider taking part in the study prior to the appointment. The PIS will provide them with information about the study and invite them to consider taking part. They will have sufficient time to read it prior to being asked to give informed consent. The patients will have as long as they feel necessary up to the end of their assessment appointment to decide whether they would like to take part and have their sockets designed with the aid of the ATFS. During their assessment appointment, they will have an opportunity to ask questions about the study to their prosthetist, and if they are happy and meet all the eligibility criteria they will be asked to read and sign a consent form. If they do not wish to take part in the study, they will continue to receive the usual care at their prosthetics centre and will be informed about this in the PIS.

At their assessment appointment, the prosthetist will take a scan of the participant's limb using a 3D scanner as per normal care. The rectification and design process was described within the prosthetists' (Group A) procedures (sections 5.4 and 5.5).

At the fitting appointment, the participant will try on their socket as per normal care with the prosthetist evaluating standard outcome measures, discussing the socket fit with the participant, and making adjustments to the socket as required. During trialling, the standard outcome measures (e.g. socket comfort scores and Key Performance Indicators (KPIs) for their clinical service) will be taken by the prosthetist. After both participant and the prosthetist are happy, the participant will take their new socket home.

This procedure matches normal care except that the socket will have been designed with the aid of the ATFS rather than the standard CAD/CAM socket design process for the clinic.

6.7 Follow-up Care

Follow-up care for participating patients to address any concerns following their fit/delivery appointment will be through existing normal standard of care pathways, i.e., planned review appointments or the patients contacting the clinic directly.

6.8 End of Study

Stage One end point

Once the final ATFS version has been reached ready for summative testing. The number of iterations required in Stage One will be determined by the technology development process (e.g., feature freeze), and the participating clinicians being comfortable to use the ATFS throughout the full socket design process independently without resorting to their current socket design process (i.e., no further observation or detection of a usability problem).

Stage Two end point

Once the ATFS has been used to support the socket design for 19 participating patients across the three sites.

7. Data analysis

Continuous data (i.e. time taken for initial rectification and socket design using the ATFS) will be summarised using mean, standard deviation, median and 25th and 75th percentiles; categorical data (i.e. socket comfort scores) will be summarised using number of events and percentages. Completion rates of the data above will be tracked.

The qualitative data collected from audio recordings will be transcribed verbatim by a University of Southampton approved subcontractor, with whom the University has a written agreement of confidentiality. A second researcher will check a sample of data transcripts against the screen capture with audio and interview recordings for accuracy, and will interrogate the validity of the coding against the raw data. The verbal content of the interviews, and the verbal and observational data of the screen capture recordings will be analysed. The data will be fully anonymised to remove any identifying (i.e., names) and confidential information. Interview data for Stage 1 and 2 will be analysed separately using thematic analysis; a flexible approach will be applied to systematically group and identify meaning within the data[13, 14], and will be useful for the more in-depth discussions within the interviews. This analytical approach will consist of a series of steps including: familiarisation with the data, a combination of hand-coding and the QSR International NVivo 11 software (http://www.qsrinternational.com/what-is-nvivo), and searching, defining and reviewing themes.

8. Adverse events and Serious Adverse Events Reporting

In accordance with MEDDEV 2.7/3 all serious adverse events (SAEs) will be fully recorded, and the competent authority in which the clinical investigation is being performed (the MHRA) will be notified by the sponsor of the clinical investigation (Radii Devices Ltd) immediately, but not later than two calendar days after awareness by the sponsor of the SAE or of new information in relation with an already reported event.

The Principal Investigator or clinic lead at participating sites will inform the sponsor of SAEs immediately, but not later than three calendar days after their awareness of the event.

Serious adverse events would be regarded as an event occurring during participation (for example an injurious fall) that:

- Leads to death or injury leading to permanent impairment to a body structure or body function.
- Leads to a serious deterioration in health of the participant that either results in:
    - A life-threatening illness or injury, or
    - A permanent impairment of a body structure or a body function, or
    - In-patient hospitalization or prolongation of existing hospitalization, or
    - In medical or surgical intervention to prevent life threatening illness

Non-serious adverse events would be regarded as an event occurring during participation reported by the patient as in their usual clinical care pathway:

- Any untoward medical occurrence (for example a socket material failure), unintended disease or injury

The trial design minimises risk as participants are following their usual care pathway for receiving a new prosthetic socket. AEs related to socket use will be naturally collected, recorded, and managed by the prosthetists as part of the usual care procedures.

A causality assessment of the relationship between the use of the medical device and any occurrence of SAEs will be carried out by the sponsor in collaboration with the clinical judgement of the Principal Investigator and clinic leads, and using relevant documents such as the investigator's brochure, the clinical investigation plan, protocol, risk analysis and device details.

For the purpose of harmonising, reporting of SAE's will be categorised according to five different levels of causality as defined in MEDDEV 2.7/3:

- Not related
- Unlikely
- Possible
- Probable
- Causal relationship

This clinical investigation minimises the risk of SAEs with a causal relationship as the standard clinical care pathway is being followed so procedures (design and fitting of a prosthetic socket) would still have been applied to the patients in the absence of the ATFS use.

9. Ethical considerations and risks

Informed consent

Written informed consent will be received from all participants prior to entry to Stage One and Stage Two of the study.
For Group A participants, the consenting process will be conducted by a member of the study research team at their respective NHS site.
For Group B participants, the consenting process will be conducted by a member of the patient's usual multidisciplinary team (MDT) (e.g. their prosthetist or the site Principal Investigator) or by one of the study research team in attendance in their normal clinical care setting, according to Good Clinical Practice (GCP) guidelines.

All prospective participants will be provided with a detailed PIS and provided the opportunity to ask any questions regarding the study. We will also emphasise that participants are free to withdraw from the study at any time without any explanation, and that doing so will not affect their treatment or care or employment in any way. Patient participants' involvement in the study will be documented in their medical record by site Principal Investigators uploading completed consent forms.

Anonymity

All participants will be allocated a study ID when recruited. This ID will be used during analysis and dissemination of the research (via journal publications or presentations) to ensure data remains anonymous.

Right to withdraw

Participants in both groups have the right to withdraw from any aspect of the study and at any time during the study without giving a reason, or any of their legal, clinical or employment rights affected. This information will be included in the PIS and consent form, and the participants will be advised of it verbally throughout the process of the study.

Data security

The research team at Cambridge University Hospitals NHS Foundation Trust, Norfolk Community Health and Care NHS Trust, North Bristol NHS Trust, University of Southampton and Radii Devices will comply will all aspects of the UK General Data Protection Regulation (UK GDPR).

Encrypted recording devices will be used as prosthetist participants use the ATFS Software, when thinking aloud, and during the interviews. Recordings will be anonymised at-source and file-naming. A transcription service officially approved by the University of Southampton (collaborating on this study) will transcribe the recordings. There is a written agreement of confidentiality (SLA) between the transcription service provider and the University of Southampton. Once transcribed, recordings

will be deleted from the recording device. The transcription data will be transferred to the study team via a secure, password-protected system.

All information collected during the course of the study will be kept strictly confidential. Information will be held securely on paper and electronically at Radii Devices Ltd, including appropriate storage, restricted access, on password protected Radii Devices machines, and disposal arrangements of patients' identifiable details on their consent form. Participants will not be identified in the results of the study. Data will be archived for a minimum period of 10 years following the end of the study. Personal data will be processed according to GDPR.

Personal Protective Equipment (PPE) considerations

PPE will be used according to each trust's Infection Prevention and Control guidelines. As the study will be integrated with usual care, PPE will be worn as per usual care. On site research activities will be undertaken by the attending study researcher and the clinical teams who usually work at each prosthetics centre and are familiar with Trust PPE guidance.

10. Study Management & Monitoring

This study will be overseen by a Chief Investigator and the study Principal Investigators at each participating site and managed by the study team members, with periodic clinical investigation meetings, as designated within the roles and responsibilities section 1.4 of 283-04A-01 (XE) Clinical Investigation Plan. Briefly, approximately weekly technical and onsite investigator meetings, and once every two month clinical investigation and grant study meetings will be held for updates and monitoring of documentation on recruitment progress, practical issues and challenges, study data and adverse events reporting, etc., to ensure effective collaborative communication and efficient progress.

For each Group B (patient) participant a study researcher will complete an E-Case Report Form (E-CRF, see Section 16.2) to check off that study activities have been carried out and that screen recording and semi-structured interview audio recordings have been saved in the master site file.

The monitoring plan can be observed within Section 12.6 of 283-04A-01 (XE) Clinical Investigation Plan. Briefly, there will be one monitoring visit at each participating site during Stage Two. A single monitoring visit at each study site was determined appropriate taking into account the low complexity and risk and minimal deviation from current clinical processes associated with this clinical investigation. Carrying out the monitoring visit at each site nearer the end of Stage Two will be carried out so that the monitor is able to verify all of the necessary consent forms and e-CRF forms.

At each monitoring visit, the monitor will have a briefing meeting (approximately one hour) with the site Principal Investigator and on-site investigators ahead of verifying consent forms and E-CRF forms as specified in Section 12.6 of 283-04A-01 (XE) Clinical Investigation Plan.

11. Schedule Of Events (SoE)

10.1 General Activities (Per Site)

Activity	Undertaken by	Study Set-up	During Study	Study Close-down
Set-Up	Study team and NHS R&D Departments			
Training	Study team and local participating staff			
Monitoring	Delegated monitor from study team and Nursing/Manager for 1 hour briefing meeting			
Close-down	Study team and NHS R&D Departments			

10.2 Stage One Per Participant Activities

			Standard Patient Visit		
Activity	**Duration (mins)**	**Undertaken by**	**Assessment Appointment**	**Check Socket Fitting Appointment**	**Definitive Socket Fitting Appointment**
Informed Consent	30	Nursing/Manager (local participating staff or Principal Investigator) or study researcher			
Use of ATFS	30	Local participating staff			
eCRF completion including data transfer and query resolution	10	Study researcher with Nursing/Manager (local participating staff or Principal Investigator) for monitoring and query resolution			

10.3 Stage Two Per Participant Activities

			Standard Patient Visit		
Activity	**Duration (mins)**	**Undertaken by**	**Assessment Appointment**	**Check Socket Fitting Appointment**	**Definitive Socket Fitting Appointment**
Informed Consent	30	Nursing/Manager (local participating staff or Principal Investigator) or study researcher			
Use of ATFS	20	Local participating staff			
eCRF completion including data transfer and query resolution	10	Study researcher with Nursing/Manager (local participating staff or Principal Investigator) for monitoring and query resolution			

12. GANTT Chart

	11/23	12/23	01/24	02/24	03/24	04/24	05/24	06/24	07/24	08/24
Ethics Approval & Setup with the NHS Trusts										
Recruitment										
Data collection										
Data analysis										
Write up										
Dissemination										

13. Approvals

Ethical approval will be obtained through IRAS (Integrated Research Application Service) from the Health Research Authority (HRA), a NHS Research Ethics Committee, and the MHRA (Medicines and Healthcare Products Regulatory Agency), because this is a clinical investigation of a medical device (IRAS ID: 317901). Study approval will also be sought from the University of Southampton Ethics Research Governance Online (ERGO, ERGO No: 81419). Radii Devices Ltd. will act as sponsor for this study.

This clinical investigation has also been approved for inclusion in the NIHR (National Institute for Health and Care Research) Clinical Research Network (CRN) Portfolio, NIHR CRN – MUSC 57956.

14. Funding

An Innovate UK Biomedical Catalyst Grant in collaboration with Opcare Ltd, University of Southampton and Radii Devices Ltd, commencing June 2022, is funding this study (reference 10014827). Qualitative and quantitative data analysis will be undertaken by the study research team.

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16. Appendices

16.1 Semi-structured Interview guide (Group A) – Appendix A

Introduction:

- *Briefly explain aims of study*
- *Briefly explain purpose of interview is to understand their views and experiences of applying the Adaptive Templates Fitting System (ATFS) to design sockets*
- *Interested in their own views and experiences*
- *There are no right or wrong answers*
- *Explain what will be done with the data collected*
- *Have they got any questions?*

Semi-structured interview questions:

1. How did you find/can you tell me about your experience of the Adaptive Templates Fitting System?
    - What do you think went well?
    - What didn't go well?
2. Did you apply any of the rectification suggestions?
    - If Yes or No, Why?
    - If Yes, Did you do any further adjustments or tweaks after applying the suggestions?
    - Is it something you would do again?
3. What are your thoughts on the socket that you fitted?
    - Differences/similarities from what you would have designed using just your clinics' standard software?
4. Did you have to make physical adjustments on the socket during the fitting appointment?
5. Did you have to make minor or major adjustments during/after the socket fitting session?
    - How did you go about this? Using TracerCAD or Radii Software?
6. What do you think about using the Adaptive Templates Fitting System software in-clinic?
    - Good and bad points
7. What factors do you think need to be considered to make this kind of technology useable in clinic?
8. What is your level of experience, i.e., years post-qualification working in prosthetics services?
    - What are your thoughts of new graduate prosthetists, for example, using such Adaptive Templates Fitting System software?

9. Is there anything else that you'd like to share regarding use of such Adaptive Templates Fitting System software including technology to support evidence-based socket design?
    - Have your views changed while participating in this study? (if end of study interview)
10. Is there anything else you would like to tell us about your experiences with socket design and fit?

16.2 Electronic Case Report Form (E-CRF) – Appendix B

283-04A-03 (XA) E-CASE REPORT FORM

Based on 283-04A-01 (XE) Radii Clinical Investigation Plan

Study title: Clinical usability evaluation of Adaptive Templates Fitting System for socket design

Details to be completed by a study researcher (one form per Group B participant):

* Required

* This form will record your name, please fill your name.

1. Group A Participant ID *

2. Group B Participant ID *

3. Date Group B Screened *

4. Date Group B Consent Received *

5. Date Group B on Study *

6. Date Group B Completed Study *

7. Socket Comfort Score(s) (date and collect from Group A participant) *

8. Screen recording files for *

- [ ] Initial design
- [ ] Subsequent design

9. Screen recordings saved in master site file *

- ◯ Yes

10. Time data for ATFS use saved in master site file *

- ◯ Yes

11. Semi-Structured interview audio recording saved in master site file *

- ◯ Yes

12. Printed name of researcher *