Nottingham University Hospitals NHS
NHS Trust

Study title:

Needle fasciotomy versus limited fasciectomy for the treatment of Dupuytren's contractures of the fingers: a feasibility study which investigates the acceptability and design of a multicentre randomised controlled trial.

Study Short Title: HAND-1

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust (s), regulatory authorities, and members of the Research Ethics Committee.

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Sponsor

Nottingham University Hospitals NHS Trust is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB)

This protocol describes the feasibility study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of changes made
MA01	1.1	27 Aug 2015	Eleanor Harrison	pg 3 Trial Coordinating Centre *'Amy Moody'* changed to *'HAND-1 Trial Manager'*. Telephone number updated. pg 8 Exclusion Criteria *'Requirement for Dermofasciectomy'* changed to *'Planned dermofasciectomy or very limited fasciectomy (excision of ≤1cm cord segment)'* to ensure consistency with pg 15 pg 15 Outcome measures *'The following questionnaires will be self-completed by participants at follow up only:* *1. Global Improvement Item (to act as the anchor for the assessment of the performance of the PROMS)'* Changed to *'The following data will be collected at follow up only:* *1. Global Improvement Item – self-completed by participants (to act as the anchor for the assessment of the performance of the PROMS)'* Page 16, '*audio-recoding'* corrected to '*audio-recording'*. Pg 16 Participant selection and enrolment. Addition of paragraph: *'If a patient presents with two or more fingers on the same hand that require treatment, then both/all fingers will be treated in the same manner (i.e. both/all with limited fasciectomy or both/all with needle fasciotomy). For any study outcomes that require reference to a single finger, we will use the one which the patient reports pre-operatively as causing the most trouble.'*
SA02	2.0	21 Jun 2016	Eleanor Harrison	pg. 11 Flow diagram of study footnote added: *'*6 month follow-up may be via postal questionnaire, depending on date of surgery'* pg. 12 Table1: Study procedures and assessments addition of footnotes: *' [4] 6 month follow-up may be carried out via post if clinic visit is not possible due to date of surgery* *[5] Questionnaire will be completed via post and assessments will not occur if 6 month follow-up is not carried out in clinic'* pg. 18 Randomisation addition of sentence: *'Photographs will only be taken and assessed for those participants who have their final 6 month follow-up in clinic.* pg18. Study Procedures. Screening and Recruitment addition of sentence: *'. Patients who consent to audio recording may pause or stop this at any time.'* pg.19 Participant Follow-up addition of paragraph: *'For some participants a 6 month clinic visit will not be possible (within the study timelines) due to the waiting time between randomisation and*

				surgery. These participants will complete a 6 month follow-up postal questionnaire only. The questionnaire will be sent by the coordinating centre with a prepaid return envelope. Participants will be informed, by the researcher, at the 6 week visit, whether they will be receiving a final 6 month follow up visit in clinic or whether they will be sent postal questionnaires by the coordinating centre. *Upon completion of all trial visits and questionnaires all participants will receive an end of study letter accompanied by an information sheet thanking them and informing them that their participation in the study is complete.'* pg19. Qualitative Methods addition within sentence: *'undertaken by researchers from the University of Bristol'* pg.20 Audio-recording of recruitment appointments addition of sentence:*'Patients may pause or stop the audio recording at any time'* pg21 Patients' experience of trial participation addition of sentence: '*Separate written consent will be obtained from participants for these interviews. The timing of this will be agreed between the researcher and interviewee.* pg.22 Patients' experience of trial participation and acceptability of interventions addition of sentence: '*Participants will be able to pause or finish the discussion with the researcher at any time, without giving a reason'* pg23. Serious Adverse Events (SAE) addition of sentence: '*SAEs that occur from time of surgery to 6-month follow-up should be reported. SAEs should be reported on the sponsor template and faxed or emailed to NCTU. Email: MS-NCTU-SAE@nottingham.ac.uk Fax: 0115 748 4091.* Pg 23 Serious Adverse Events (SAE) Amendment of sentence: *'All SAEs will be reported to the Chief Investigator within one working day and to the sponsor within 15 days.'* to *'All SAEs will be reported to the Chief Investigator within one working day of receipt of SAE report and to the sponsor within 15 days of receipt of SAE report.'*

PROTOCOL APPROVAL

Needle fasciotomy versus limited fasciectomy for the treatment of Dupuytren's contractures of the fingers: a feasibility study which investigates the acceptability and design of a multicentre randomised controlled trial.

Tim Davis	T N Davis	2/8/16
Chief Investigator	Signature	Date
Alan Montgomery	A. Montgomery.	25/7/2016.
Trial Statistician	Signature	Date
Maria Koufali		29/7/2016
Sponsor Representative	Signature	Date

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CRF	Case Report Form
CRPS	Complex Regional Pain Syndrome
DASH	Disabilities of the Arm, Shoulder and Hand Questionnaire
DIP	Distal Interphalangeal joint
GCP	Good Clinical Practice
GP	General Practitioner
GRI	Guyatt's Responsiveness Index
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File
LF	Limited Fasciectomy
LPLV	Last patient last visit
MCIP	Minimal Clinically Important Difference
MCP	Metacarpophalangeal joint
NF	Needle Fasciotomy
NUH	Nottingham University Hospitals NHS Trust
PEM	Patient Evaluation Measure
PIS	Participant Information Sheet
PIP	Proximal Interphalangeal joint
PPI	Public Patient Involvement
PROMS	Patient Reported Outcome Measures
QRI	Qualitative Recruitment Intervention
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SRM	Standardised Response Mean
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
UAR	Unexpected Adverse Reaction
URAM	Unité Rhumatologique des Affections de la Main Questionnaire

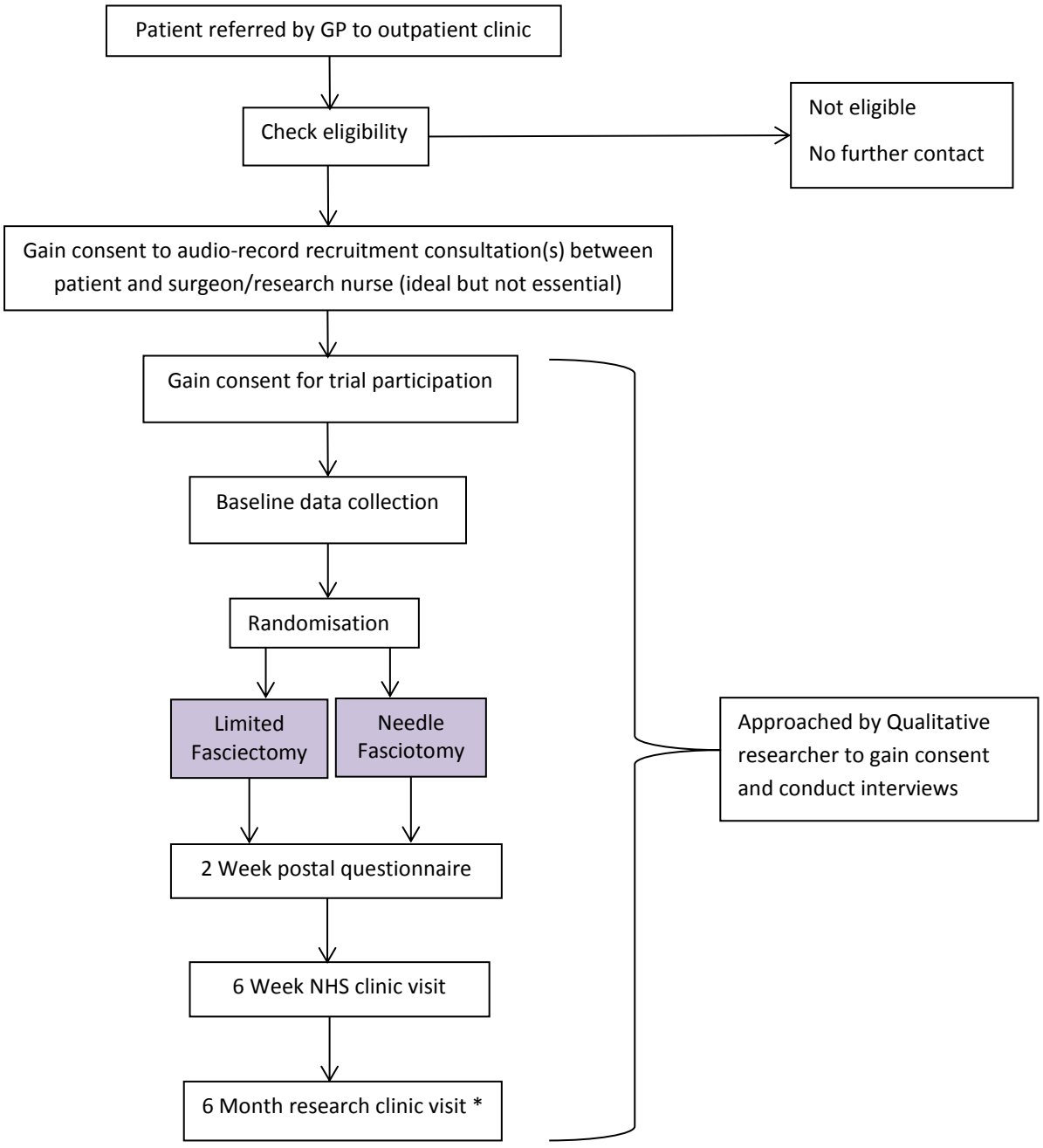
KEYWORDS
Dupuytren's contracture, Limited Fasciectomy, Needle fasciotomy, Feasibility, Randomised controlled trial

STUDY SUMMARY

Title	Needle fasciotomy versus limited fasciectomy for the treatment of Dupuytren's contractures of the fingers: a feasibility study which investigates the acceptability and design of a multicentre randomised controlled trial (RCT).
Short title	HAND-1
Chief Investigator	Professor Tim Davis
Objectives	To investigate the feasibility and acceptability of conducting a randomised controlled trial (RCT) to compare the clinical and cost effectiveness of needle fasciotomy with limited fasciectomy for the treatment of Dupuytren's contractures of fingers.
Study Configuration	Feasibility randomised controlled trial.
Setting	Three secondary care centres recruiting patients at Nottingham University Hospitals NHS Trust/Nottingham Treatment Centre, Derby NHS Foundation Trust and Wrightington, Wigan and Leigh NHS Foundation Trust.
Sample size estimate	As this is a feasibility study, a formal sample size calculation for between group comparisons of a primary outcome is not appropriate.
Number of participants	50-85 in total from three sites.
Eligibility criteria	Adults referred from primary care with Dupuytren's contractures of the fingers. **INCLUSION CRITERIA** 1. Aged over 18 years. 2. One or more fingers with a Dupuytren's contracture of >30° in the metacarpophalangeal (MCP) and/or proximal interphalangeal joints (PIP). 3. Well defined cord(s) causing contracture. 4. No previous surgery for Dupuytren's contracture on the same hand. 5. Willing to undergo either study procedure. 6. Able to complete follow up assessments. **EXCLUSION CRITERIA** 1. Dupuytren's contracture of the distal interphalangeal joints (DIP) only. 2. Planned dermofasciectomy or very limited fasciectomy (excision of ≤1cm cord segment). 3. Previously recruited into this study for treatment of either hand. 4. Life expectancy less than 3 years.
Description of interventions	**Intervention: Needle Fasciotomy** This procedure takes place in an outpatient clinic room setting. The contracture is divided with a needle which pierces the skin (no skin incision). **Standard Care: Limited Fasciectomy** This procedure takes place in an operating theatre under regional or general anaesthesia. The contracture is surgically removed via an incision.

Duration of study	22 months
Outcome measures	Feasibility outcomes relating to participant recruitment, treatment and follow up; clinical and patient reported outcomes; treatment and patient reported costs; acceptability of treatment/ study related procedures.
Statistical methods	Data analysis will primarily be descriptive to address the feasibility aims of the study. All analyses will be documented in a Statistical Analysis Plan which will be finalised prior to database lock. All analyses will be carried out using Stata 13 or above.

Flow diagram of study



*6 month follow-up may be via postal questionnaire, depending on date of surgery

Table 1: Study procedures and assessments

	Screening and enrolment[1]	Day of Surgery	2 Weeks post-surgery (postal questionnaire)	6 Weeks post-surgery (routine NHS clinic visit)	6 Months post-surgery (research clinic visit)[4]
Screen for eligibility and obtain written consent for audio recording consultation	X				
Audio recording of consultation	X				
Obtain written consent for trial	X				
Patient-completed questionnaires	X	X[2]	X	X	X[5]
Hand assessment: extension in affected finger(s) grip strength	X			X	X[5]
Photographic assessment	X				X[5]
Randomise	X				
Conduct allocated procedure		X			
Record details of procedure performed		X			
NHS hospital resource use data extracted from medical record					X
Interviews with consented individuals (staff and patients)	X[3]				X

[1] Participant consent for the trial, baseline assessment, and randomisation may take place at the first clinic visit or at a further visit arranged with the research nurse/assistant

[2] Patient Evaluation Measure (PEM) only

[3] Interviews will take place throughout the study from consent up until 6 months

[4] 6 month follow-up may be carried out via post if clinic visit is not possible due to date of surgery

[5] Questionnaire will be completed via post and assessments will not occur if 6 month follow-up is not carried out in clinic

INTRODUCTION
BACKGROUND

Dupuytren's contractures are fibrous cords under the skin of the palm of the hand. They typically occur in men and women over 50. They have a strong genetic tendency and increased incidence associated with diabetes and epilepsy (1).

The contractures are painless but cause one or more fingers to gradually and irreversibly curl into the palm, resulting in loss of hand function for day-to day tasks such as washing, grooming and shaking hands. It increasingly becomes difficult to put on a glove, hold large objects or put the hand in a pocket. Disabilities experienced are diverse and include difficulties with computer use, baking, piano playing, carpentry, gardening, cycling and sports such as golf and tennis (2, 3). The standard treatment is surgery to remove or divide the Dupuytren's contractures, allowing the finger to straighten (extend) again. Surgery, however, does not cure Dupuytren's contractures, and recurrent contractures may require further surgery.

The standard treatment is surgery and approximately 16,000 operations costing £50 million were performed for Dupuytren's contractures in operating theatres in England in 2011-12 (4). This has increased by 23% over the past five years (4). Increased longevity in an aging population may cause a 77% increase in demand for treatment by 2030 (5).

However there are no agreed guidelines for surgical treatment of Dupuytren's contractures. The most common operation is a **"limited fasciectomy" (LF)**, in which the fibrous cords preventing the finger(s) from straightening are cut out of the hand through a long skin incision. This procedure is done under general or regional anaesthesia in an operating theatre, has a 4-6 week recovery period and is costly. Around 14,000 LFs were done in England in 2011-2012 (4). A common alternative treatment is **"needle fasciotomy" (NF)**. In this procedure the fibrous cords preventing the finger(s) from straightening are simply divided with the sharp tip of a needle without the need for a skin incision as the needle is simply passed through the skin into the underlying fibrous cord. It can be done in an outpatient clinic room and has a 1-2 week recovery period. About 1200 needle fasciotomies were performed in operating theatres during 2011/2 (4) and more will have been performed in outpatient rooms (not accurately captured by Hospital Episode Statistics).

Compared with LF, NF is less expensive for the NHS, less disruptive for patients, and probably carries a lower risk of complications that restrict hand function (temporarily or permanently) after the surgery (6). Contractures can reform in the operated fingers after either treatment, causing the finger to bend up into the palm again, but recurrence is quicker and more frequent with NF, resulting in a need for further treatment (7). Both procedures successfully straighten fingers with a Dupuytren's contracture involving only the metacarpophalangeal joint. However fingers with contractures involving the proximal interphalangeal cannot always be fully straightened with surgery.

RATIONALE FOR CURRENT STUDY

A systematic review found only five randomised or pseudo-randomised trials concerning the surgical treatment of Dupuytren's contracture (8), and a subsequent Cochrane review is in the final stages of the editorial process (9, 10). These existing studies have a number of limitations, most importantly high risk of performance and detection biases, and use of angle measurements of finger straightness and recurrence as primary outcomes rather than complications, hand function, or other patient reported outcome measures. None assessed the cost of treatments to either providers or patients,

and none examined the relative effectiveness of NF and LF in Dupuytren's contractures affecting only the metacarpophalangeal joint (around 40% of all contractures).

There is little information on the use of patient reported outcome measures (PROMs) to assess the outcome of Dupuytren's contracture treatment. Most PROMs used in hand surgery are not specific to this condition. Thirteen small studies (four retrospective and six prospective cohort and three low quality RCTs) have assessed PROMs for Dupuytren's contracture, they used: the DASH (11 studies), QuickDASH, PEM, and URAM (1 study each). Although improvements in hand function have been recorded with all after surgery, the minimal clinically important difference (MCID) for patients with Dupuytren's contractures has only been calculated for the URAM.

The lack of well-designed and conducted trials means that the choice of treatment for Dupuytren's contractures of the fingers mainly depends on surgeon and patient preference. A survey of 116 hand surgeons showed marked variations in treatments advised for Dupuytren's contractures (11). The same surgeons reported that the most important research question about surgical treatment was a comparison of needle fasciotomy with limited fasciectomy. This is also an important question for patients. A recent survey (12, 13) of 110 patients awaiting surgery found that the most important factor in deciding which treatment to have was recurrence (38%), speed of recovery following surgery (25%), or following surgeon guidance (37%). There is an urgent need for robust evidence to guide decision making.

In summary, a definitive trial comparing the outcomes and costs of needle fasciotomy with limited fasciectomy is needed. However before this can be performed a feasibility study is required. A feasibility study will provide data essential to design and conduct a future trial, including information about numbers of eligible patients, recruitment and randomisation, completion of follow up, and selection of appropriate outcome measures.

STUDY AIM AND OBJECTIVES

AIM

The aim of this study is to establish the feasibility and acceptability of conducting a large multicentre randomised trial to assess the clinical and cost effectiveness of needle fasciotomy versus limited fasciectomy for treatment of Dupuytren's contracture.

OBJECTIVES

The objectives are to:

1. Define the eligibility criteria for the future definitive randomised trial comparing needle fasciotomy with limited fasciectomy
2. Estimate the proportion of referred NHS patients with Dupuytren's contractures who meet these eligibility criteria
3. Determine the willingness of surgeons to recruit patients with different patterns of Dupuytren's contractures of the fingers
4. Estimate the proportion of eligible patients that consent to randomisation
5. Assess and optimise the recruitment process and patient pathway using integrated qualitative research
6. Estimate follow up and outcome completion rates
7. Evaluate outcomes for use as primary and secondary outcomes in the definitive study.
8. Assess and compare validity and reproducibility of two methods of measurement of finger straightness which can be performed by a research assistant
9. Determine standard practice and equipment for clinic room provision of treatment.

10. Assess the relationship between angular measurements of the finger deformity and patients' reported outcomes
11. Evaluate the utility and acceptability of health resource use questionnaires to assess the impact of care on health service use and productivity
12. Assess participant and staff views on trial conduct, trial participation, and acceptability of interventions using qualitative research methods
13. Estimate the sample size required for a definitive study

STUDY DESIGN

Design

A parallel, two arm randomised feasibility trial with participants individually allocated on a 1:1 ratio to treatment with either:

1. limited fasciectomy in the operating theatre, or
2. needle fasciotomy in a clinic room

The study will inform the design and conduct of a full trial to compare the clinical and cost effectiveness of the two treatments. Data will be used to optimise the recruitment process, monitor recovery and outcome of the treatment, assess the patient experience of the selected treatment and assess the relative benefits of different outcome measures. The duration of the study is 22 months.

Target Population

Adults referred from primary care with Dupuytren's contractures of a hand to one of three secondary care sites (Derby Hospitals NHS Trust, Wrightington, Wigan and Leigh NHS Foundation Trust and Nottingham University Hospitals/Nottingham Treatment Centre).

OUTCOME MEASURES

Feasibility outcomes are:

1. number and proportion of a) patients assessed for eligibility; b) eligible patients who consent; c) consented patients that are randomised
2. adherence by surgeons and patients with allocated treatment
3. completion of follow up assessments
4. identification of appropriate primary outcome(s) for the main trial, with estimates of clinically important effect sizes, variance, and extent of clustering by surgeon

The primary outcome measure in the planned larger RCT comparing the outcomes of these two treatments for Dupuytren's contractures will be a patient reported outcome measure (PROM). Several PROMs are used in Hand Surgery, but it is unclear which is best for Dupuytren's contractures. This is particularly as Dupuytren's contractures cause painless loss of function, whereas most hand conditions (e.g. osteoarthritis) cause loss of function due to pain. We need to assess which of the following questionnaires are best suited for the study of this condition in which people have very different functional losses (i.e. inability to wear gloves, inability to play the piano) and treatment goals. All questionnaires will be self-completed by participants at baseline and follow up:

1. Unité Rhumatologique des Affections de la Main (URAM) (14)
2. Disabilities of the Arm, Shoulder and Hand Questionnaire (DASH) (15, 16)
3. Patient Evaluation Measure (PEM) (17)*
4. Measure Yourself Medical Outcome Profile (MYMOP) (18)

5. EQ5D-5L (19)

* PEM will also be completed on the day of surgery prior to the patient receiving treatment. Waiting time between randomisation and surgery may differ for LF and NF. Completion of the PEM provides a check whether symptoms have progressed differentially during this period.

The following data will be collected at follow up only:

2. Global Improvement Item (18) – self-completed by participants (to act as the anchor for the assessment of the performance of the PROMS)
2. Complications following surgery
3. NHS resource use
4. Return to work / usual activities

The following outcomes will be measured during baseline and follow up clinic visits:

1. Grip strength
2. Angular measurement of finger straightness, with photographs taken for blinded assessment

INCLUSION CRITERIA

1. Aged over 18 years.
2. One or more fingers with a Dupuytren's contracture of >30° in the metacarpophalangeal (MCP) and/or proximal interphalangeal joints (PIP).
3. Well defined cord(s) causing contracture.
4. No previous surgery for Dupuytren's contracture on the same hand.
5. Willing to undergo either study procedure.
6. Able to complete follow up assessments.

EXCLUSION CRITERIA

1. Dupuytren's contracture of the distal interphalangeal joints (DIP) only.
2. Planned dermofasciectomy or very limited fasciectomy (excision of ≤1cm cord segment).
3. Previously recruited into this study for treatment of either hand.
4. Life expectancy less than 3 years.

WITHDRAWAL CRITERIA

Participants can withdraw from the study at any time, without giving a reason. Data already collected will be included in the analysis, unless participants specifically request that their data not be used.

STUDY INTERVENTIONS

The two surgical procedures being compared are described below. All participating surgeons will provide treatment to patients in both arms of the study.

Needle fasciotomy

This will be performed in a clinic room (not an operating theatre) equipped with a good "clinic room" spotlight, wound swabs, a couch and possibly an arm board. The hand will be rested on a rolled up towel or other object to allow full extension of the affected finger (to put the cord under tension). The cord must only be cut and no segment must be excised. A small amount of local anaesthetic is injected at the site of each point of division of the cord. The number of points along the cord at which division is attempted is at the discretion of the surgeon. The choice of needle size is at the discretion of the surgeon, and use of a knife is permitted, but no tourniquet or other surgical

instruments are allowed. Either a multiple stabbing technique or a side to side cutting action can be used to divide the cord(s) in as many places as indicated.

Limited fasciectomy

The planned operation must be a limited fasciectomy (excision of >1cm of cord), and not a very limited fasciectomy or a dermofasciectomy. This will be performed under either general or regional anaesthetic with use of a tourniquet. The contracture is exposed through a standard surgical incision. For contractures involving the metacarpophalangeal joint the Dupuytren's cord must be excised proximally to at least the proximal margin of the transverse fibres of the palmar aponeurosis. Digital cords should be excised completely from their origin. In all cases the distal margin of the cord excision should be the insertion of the cord onto the flexor sheath (or other structure). Deviations from "limited fasciectomy" (for example, a decision made during surgery based on unexpected operative findings to use a skin graft) will be logged, as will the use of additional procedures such as release of a joint contracture.

PARTICIPANT SELECTION AND ENROLMENT

All patients who are referred by their GP to the hand surgery outpatient clinic will be sent a short leaflet explaining Dupuytren's contracture of the fingers and that if they have this condition they may be invited to participate in the study during their clinic visit. The leaflet will also explain that if they are potentially suitable for the study, they may be asked for permission to audio-record consultations with the surgeon and research nurse/assistant during the clinic visit.

Posters about the trial will be displayed in waiting areas in the clinic, with participant information leaflets also available. All patients who have been referred by their GP with Dupuytren's contracture will be asked when they arrive in the clinic for permission to audio-record their consultations with the surgeon and research nurse/assistant. If they give permission they will be asked to complete an audio-recording consent form.

Patients with a Dupuytren's contracture who wish to have surgical treatment for their condition will have the trial explained to them during their initial consultation with the surgeon. If the patient is willing to consider participation, they will be given the participant information leaflet and will be offered the opportunity to discuss the study with the research nurse/research assistant during the same clinic visit. Patients will have time to consider the study and to ask any questions they might have. Those who wish to participate will be invited to provide written informed consent. This may be either later on the same day (after the patient has had time to consider participation), or the patient can return another time to see the research nurse/research assistant.

If a patient presents with two or more fingers on the same hand that require treatment, then both/all fingers will be treated in the same manner (i.e. both/all with limited fasciectomy or both/all with needle fasciotomy). For any study outcomes that require reference to a single finger, we will use the one which the patient reports pre-operatively as causing the most trouble.

Once the patient has given written informed consent, they will be asked to complete the baseline questionnaires and will have their hand and finger angles measured and photographed. They will then be randomised.

RANDOMISATION

Participants will be randomly allocated to treatment on the day they consent to participate in the study. Allocation will be in a 1:1 ratio via a secure web based system which is maintained by the Nottingham Clinical Trials Unit in accordance with their standard operating procedure.

Randomisation will be stratified by research site and the joint(s) affected with Dupuytren's contracture, and will use computer generated permuted balanced blocks of randomly varying size. Participants and their GPs will be notified of allocated treatment by letters sent from each clinic, and a copy will also be included in the medical notes.

After randomisation participants will join the NHS waiting list for their treatment so there will be a delay (potentially of up to 2 months), after randomisation. As final follow up in this feasibility study is relatively short term, timing of follow up will be from the day of treatment rather than day of randomisation.

Blinding of the surgeon and participant is not possible as it will be clear which treatment the participant received. Photographic evidence of contracture at the 6 month follow up will be assessed by a blinded assessor, with the participant wearing latex fingerless gloves to hide the surgical scars and being asked not to discuss their procedure with the researcher. Photographs will only be taken and assessed for those participants who have their final 6 month follow-up in clinic.

STUDY PROCEDURES

Screening and recruitment

All patients referred to the hand surgery clinic with a Dupuytren's contracture of the fingers will be recorded on a screening log. On arrival at the clinic, patients that have a Dupuytren's contracture will be given an information sheet about audio-recording their consultations with the surgeon and research nurse/assistant and asked for their consent. This will help us understand and optimise recruitment to the study. Patients who consent to audio recording may pause or stop this at any time. Patients who meet the inclusion criteria will be given an information sheet and will have the opportunity to discuss the study with both the surgeon and a research nurse/research assistant. Patients will have time to consider the study and to ask questions. Those who wish to participate will be invited to provide written informed consent either the same day or at a later date.

Once the patient has given written informed consent, the baseline assessments will be completed and the participant will then be randomised. The participant will be informed in writing which treatment they have been allocated and placed on the NHS waiting list, and their GP will be notified.

Treatment of participants

The surgical procedure will be carried out by a competent surgeon (consultant or experienced trainee, or inexperienced trainee under direct supervision of his/her trainer). We will record who conducted the treatment and their level of experience. Participants will receive either needle fasciotomy, or limited fasciectomy.

Following each procedure, the surgeon and/or researcher will record the following details: surgeon(s) who performed the procedure; type of procedure conducted (NF or LF); extent and definition of contracture(s) before treatment; joint contracture release or not; improvement in finger extension; wound closure technique.

In a subsample of patients receiving needle fasciotomy, or limited fasciectomy (approximately 5 of each) a researcher will observe and record more detailed information about the resources used for the procedure. This will include medical devices (e.g. anaesthetic machine, monitors); personnel (including time present and grade); reusable instruments (e.g. knife); and disposables (e.g. anaesthetic agents). We will use this information to 'micro-cost' each procedure.

Participant follow up

Two weeks after treatment, participants will be sent postal questionnaires by the coordinating centre. A prepaid return envelope will be enclosed to return the questionnaires.

If questionnaires are not returned a reminder letter or telephone call will be made to follow up, the questionnaire will be re-sent if necessary.
Six weeks after treatment, participants will attend their routine outpatient NHS clinic for a follow up appointment. During this visit they will be asked to complete the same set of questionnaires that were posted at two weeks.

Six months after treatment, participants will have an outpatient research clinic appointment. During this visit they will be asked again to complete the study questionnaires, and will have their hand and finger angles measured and photographed. As this appointment is not part of their NHS care, participants will be able to claim travel expenses for this visit only. For some participants a 6 month clinic visit will not be possible (within the study timelines) due to the waiting time between randomisation and surgery. These participants will complete a 6 month follow-up postal questionnaire only. The questionnaire will be sent by the coordinating centre with a prepaid return envelope. Participants will be informed, by the researcher, at the 6 week visit, whether they will be receiving a final 6 month follow up visit in clinic or whether they will be sent postal questionnaires by the coordinating centre.

Upon completion of all trial visits and questionnaires all participants will receive an end of study letter accompanied by an information sheet thanking them and informing them that their participation in the study is complete.

At the end of the trial follow up period, we will extract information from the hospital medical record system onto a CRF to record any further outpatient appointments, outpatient procedures, emergency department visits or inpatient admissions related to the study hand in the 6 months after the initial procedure.

QUALITATIVE METHODS

Qualitative research, undertaken by researchers from the University of Bristol, will be integrated into the HAND-1 RCT feasibility study to provide fundamental insights into the feasibility and design of a main trial. It will focus on two key aspects:

1. Understanding and optimising the recruitment to trial process
2. Exploring patients' experience of trial participation and acceptability of interventions

1. Quintet Recruitment Intervention to understand and optimise the recruitment to trial process

A Quintet Recruitment Intervention (QRI) will be implemented in the HAND-1 feasibility study to optimise trial recruitment. This method was developed initially in the ProtecT (Prostate testing for cancer and Treatment) study (20, 21) and has subsequently been used and further refined in a number of completed and ongoing RCTs (22-26). The aim of the QRI is to understand the recruitment process and how it operates in each of the clinical centres. Sources of recruitment difficulties can then be identified and suggestions made to change aspects of the design, conduct, organisation or training that could then lead on to improvements in recruitment. The QRI will be flexible in its intensity and comprehensiveness to operate in the most effective way for the feasibility study. It will be undertaken in three distinct but overlapping phases:

Phase 1: Understanding recruitment

The aim of Phase 1 is to understand the recruitment process as it occurs. There are several distinct parts that can provide information about recruitment as it happens, and to identify and investigate the sources of recruitment difficulties. A multi-faceted, flexible approach will be adopted, using one or more of the following methods until the point of data saturation – when new data does not materially add to the findings:

1. Monitoring the patient pathway through eligibility and recruitment

Comprehensive logging of potential trial participants through screening and eligibility phases is helpful to monitor recruitment. All of the three study centres will therefore be asked to maintain detailed trial screening logs. This will record the details of patients who are or are not screened for trial entry, reasons for ineligibility and details of eligible patients who do not consent to trial participation and randomisation. These logs will be monitored regularly to identify patterns relating to recruitment rates, reasons for ineligibility, and points at which patients do not continue with trial recruitment. Analysing screening logs has the potential to highlight problems early on in the process of trial recruitment.

2. Audio-recording of recruitment appointments

All consultations in which the trial is discussed and the patient is offered participation in the trial will be audio-recorded following patient consent to do so. This will primarily be the initial consultation between patient and surgeon, but may include further discussions with the surgeon, as well as consultations with the research nurse/assistant or any other relevant clinic staff. The audio recordings will be used to explore information provision, recruitment techniques, patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision. The study centres will be provided with digital audio-recorders, guidance on how to use them and a discussion of the importance and rationale behind the audio-recordings. Patients may pause or stop the audio recording at any time. The qualitative researcher will listen to appointments and document relevant details which will form the basis for individual confidential feedback and trial-specific training.

3. Semi-structured interviews

a. Semi-structured interviews will be conducted with the trial recruiters at various time points to assess their views on the trial and its conduct, including knowledge of the evidence and personal views about the interventions, how they explain the study to patients and perceived barriers to recruitment. This can help to highlight possible recruitment difficulties.

b. Members of the Trial management group (TMG), including the CI and those most closely involved in the design, management, and co-ordination of the trial, may also be interviewed to ascertain their involvement in the trial and their thoughts on it to help understand the recruitment process and identify possible areas of difficulties.

c. Interviews will also be undertaken with a purposeful sample of up to 30 eligible patients soon after the offer of trial participation to explore their views on the trial and recruitment process, presentation of study information, study documentation and reasons for accepting or declining randomisation. A maximum variation sampling strategy will be employed to ensure we capture a broad range of patients.

Interview topic guides will be used to ensure similar areas are covered in each interview within each group, based on those used in previous studies, but will be sufficiently flexible to encourage the informants to express their own views about the study and any recruitment challenges expected or

experienced. Informants in group (a) who directly recruit to the trial will also be asked about their knowledge of the evidence and personal views about the trial treatments, how they explain the study to patients, and their views about barriers to recruitment. Those in group (b) will be asked about their involvement in the trial and recruitment, and informants in group (c) will be asked to discuss their views about the presentation of study information and the acceptability of randomisation.

4. *Observations of investigator meetings*

The qualitative researcher may observe and possibly audio-record meetings between the CI, TMG and clinical investigators to discuss progress with the trial. The aim will be to gather information about specific issues that may have a bearing on recruitment.

5. Study documentation

Patient information sheets (PIS) and consent forms will be scrutinised by the qualitative researcher and patients to identify aspects that are unclear or potentially open to misinterpretation. They will be compared with the findings from the interviews and recorded appointments to identify any disparities or improvements that could be made.

Phase 2: Feedback to study team and plan of action

The qualitative team will present summaries of anonymised findings from Phase 1 to the CI (and TMG if agreed by CI), highlighting any factors that appear to be affecting recruitment with supporting evidence. It is likely that some aspects will be generic, such as how to explain randomisation and deal with patient preferences, as well as issues specific to the HAND-1 feasibility RCT. A plan of action will then be drawn up to optimise recruitment. This may include training sessions for recruiters, in which results are fed back and areas of difficulties addressed, recruitment tips documents, re-drafting study information to provide balanced information and changing aspects of organisation in clinical centres.

Phase 3: Evaluation of the impact of the plan

Numbers of eligible patients, and the percentages of these that are approached about the RCT, consent to be randomised and immediately accept or reject the allocation will be assessed before the plan of action is implemented, and regularly afterwards to check whether rates are improving.
Follow up interviews may also be conducted with the trial recruiters to ascertain their views on the acceptability of the QRI and any changes that may have occurred as a result.

2. Patients' experience of trial participation and acceptability of interventions

In addition to optimising recruitment, qualitative research methods will also be used to explore patients' experience of trial participation and acceptability of the study treatments. Semi-structured interviews will be undertaken with up to 30 trial participants up to six months after treatment to understand their experience with and acceptability of the treatment, outcome measures and wider trial processes. Separate written consent will be obtained from participants for these interviews. The timing of this will be agreed between the researcher and interviewee. The final sample size will be driven by data saturation. Where possible, patients who were interviewed earlier on in the trial will be contacted for this follow-up interview, or new patients will be purposefully sampled to ensure a broad range of participants. Topic guides will be used to ensure similar topics are covered in each interview but applied in a flexible manner enabling issues of importance to the patients to emerge. The guide will focus on their experiences of living with Dupuytren's contracture pre and post intervention, previous experiences of treatment, recovery post intervention, views on the treatment

received, the suitability and ease of understanding and completing the hand function outcome measures, and their reflections of participating in the trial. Participants will be able to pause or finish the discussion with the researcher at any time, without giving a reason

Qualitative data analysis

Interviews and recruitment consultations will be audio-recorded, fully transcribed and, along with recruitment screening logs and observations, subject to simple counts, content, thematic and targeted conversation analyses. Preliminary analysis will be used to inform training and further data collection. Members of the qualitative team will independently analyse a proportion of transcripts to assess the dependability of coding, and will meet regularly to review coding and descriptive findings, agree further sampling and training strategies, and discuss theoretical development – all in close collaboration with the CI. Results from the qualitative research will help inform the optimal design of a full scale randomised trial.

ADVERSE EVENTS

Adverse Events (AE)
Both interventions being evaluated in this study are minor surgical procedures that are widely available within the NHS. Adverse events that could be due to the surgical procedures are therefore outcomes for the study. Data on these events will be recorded on the case report forms.

Serious Adverse Events (SAE)
A Serious Adverse Event is defined as any untoward and/or unexpected medical occurrence or affect that:

- Results in death
- Is life-threatening – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

For the purpose of this trial, the following SAEs will be considered reportable:

- Death
- Loss of finger
- Any unexpected and serious event that is potentially related to the intervention

SAEs that occur from time of surgery to 6-month follow-up should be reported. SAEs should be reported on the sponsor template form and faxed or emailed to NCTU.
Email: MS-NCTU-SAE@nottingham.ac.uk Fax: 0115 748 4091

Any SAE that is not a death will be followed until there is resolution or the event is considered stable. All SAEs will be reported to the Chief Investigator within one working day of receipt of SAE report and to the sponsor within 15 days of receipt of SAE report.

STATISTICS AND DATA ANALYSIS

Estimated sample size

As this is a feasibility study, a formal sample size calculation for estimating between-group effects is not appropriate. The aim is to recruit 50-85 participants based on the following assumptions: three centres performing a total of 600 treatments for Dupuytren's contractures during the 12 month recruitment period, estimated 65% eligible, giving a total of approximately 400 patients who will be invited to participate. One of the primary aims of this feasibility study is to estimate response to invitation, eligibility, consent, randomisation and follow-up. Based on the total number invited, estimated margins of error for these proportions will range between 5% and 13%.

Data analysis

A Statistical Analysis Plan will be agreed prior to database lock and data analysis. A CONSORT flow diagram showing the numbers of people approached, eligible, recruited and randomised (with reasons for exclusions) will be produced. Recruitment rates at the start and end (after modification of the recruitment method based on the qualitative studies) of the recruitment phase of the study will be compared. Numbers and characteristics of participants recruited will be summarised using appropriate descriptive statistics, and compared with patients who were eligible but not randomised. Completeness of data collection will be compared between trial arms. Descriptive summaries of outcome data at each follow up time point will be presented. We will check outcome distributions for suggested floor and ceiling effects, and we will estimate intra-cluster correlation coefficients by surgeon.

We will use direct observation of the procedures to produce a 'micro-cost' estimate (27) for needle fasciotomy and limited fasciectomy by combining resource use with unit costs provided by the hospital finance departments (28). We will use standard unit costs to estimate the NHS costs of care in the 6 months post-procedure. Descriptive summaries of NHS cost data at each follow up time point will be presented (29).

Minimum clinically important effects for each PROM will be estimated using three anchor-based responsiveness statistics: (i) standardised response mean (SRM); (ii) effect size (ES); (iii) Guyatt's Responsiveness Index (GRI). This analysis will guide the choice of PROM for use in a definitive trial of treatment of Dupuytren's disease, along with participant ranking of the different PROMs.
Improvements in ability to extend finger(s) after surgery will be compared with these responsiveness indices to investigate its use as a surrogate measure of hand function and calculate its minimum clinically important difference.

Data and all appropriate documentation will be stored for a minimum of five years after the completion of the study, including the follow-up period.

STUDY MANAGEMENT

The Chief Investigator will have overall responsibility for the trial, supported by the Trial Management Group (TMG). The TMG will have responsibility for day-to-day management of the study: monitoring progress of the study against targets, especially recruitment and retention; compliance with study protocol and procedures; data quality and completeness; and ensure prompt analysis and reporting. The TMG will meet every 1-2 months. A Trial Manager will oversee the day-to-day running of the trial, and support the sites. An independent Trial Steering Committee (TSC) comprising of members with appropriate expertise (for example, clinician/hand surgeon, statistician and PPI representative) will provide independent oversight of the study, including monitoring

progress against targets, advising the Chief Investigator and TMG, and providing an independent assessment of whether a full trial is feasible.

The TSC will meet initially to review and agree the protocol, and thereafter every 6 months. As both interventions in the feasibility study are within current NHS practice, safety oversight will be undertaken by the TSC, without the need for an independent Data Monitoring Committee.

FUNDING

This study is funded by the National Institute for Health Research (NIHR) Research for Patient Benefit programme.

QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted according to the Quality Management System at the NCTU. The study may be subject to inspection and audit by Nottingham University Hospitals under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

Monitoring of study data will be by a combination of central and on-site monitoring, in accordance with the risk-based monitoring plan agreed before the trial commences.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

GOOD CLINICAL PRACTICE

ETHICAL CONDUCT OF THE STUDY

The study will be initiated only after the protocol, consent forms and participant information sheets have received approval from the REC and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 2013; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

CONFIDENTIALITY

Information about participants will be stored anonymously, confidentially and securely, and will be managed according to the requirements of the Data Protection Act, NHS Caldicott Guardian and Research Governance Framework for Health and Social Care, conditions of REC approval and NHS information governance policy.

A unique identification number will be automatically attributed to each participant randomised in the study.

Study data will be held at the University of Nottingham, but will be shared with the University of Bristol and other organisations as relevant.

DATA PROTECTION

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality.

Access to collated participant data will be restricted to the CI and appropriate study staff. Participants will give optional written consent if they are happy for this data to be used in future studies.
Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

INDEMNITY

Nottingham University Hospitals NHS Trust will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study. Standard NHS indemnity applies.

STUDY CONDUCT AND RESPONSIBILITIES

PROTOCOL AMENDMENT, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study documents will not be implemented without these approvals.

In the event that the CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately.

RECORD RETENTION AND ARCHIVING

In compliance with ICH/GCP guidelines, regulations and in accordance with the Nottingham University Hospital standard operating procedures (SOP) and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained at each site for at least 5 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the CI on behalf of the Sponsor shall be finally archived at secure archive facilities. This archive shall include all anonymised audio recordings, study databases and associated meta-data encryption codes.

END OF STUDY

The end of study is defined as the end of funding as per the grant. The Sponsor or CI has the right at any time to terminate the study for clinical or administrative reasons.
The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

On completion of the study, a clinical study report will be prepared.

PUBLICATION POLICY

The trial results will be published in a peer reviewed journal, and presented at scientific meetings. Reporting will be in compliance with CONSORT recommendations. Results will be made available to participants through a newsletter (unless they have stated they do not wish to receive this).
The trial results will be published by named members of the trial team, on behalf of the HAND-1 Study Collaborative Group. Members of the collaborative group will be listed in the publication, based on contributorship. Any secondary publications may be published by named individuals, but with appropriate acknowledgement of the collaborative group.

PATIENT AND PUBLIC INVOLVEMENT

Our team includes a patient representative who has undergone surgical treatment for Dupuytren's contractures, and who will contribute to the management and analysis and reporting of the study.

SIGNATURE PAGE

Signatories to Protocol:

Chief Investigator: Prof Tim Davis

Signature: 

Date: 26th July 2016

Principal Investigator: _____

Signature: _____

Date: _____

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