icons II

Identifying Continence OptioNs after Stroke

PROTOCOL

A UK Collaborative Study funded by the
NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC),
Health Technology Assessment (HTA) Programme

Funded by NHS National Institute for Health Research

Funding acknowledgement: This research was funded by the NIHR HTA (16/111/31)
Department of Health disclaimer: The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health

Sponsor

Name:	Professor StJohn Crean
Address:	Ethics and Integrity Unit, Research Services, Foster Building FB033 – Basement, University of Central Lancashire, Preston, PR1 2HE
Telephone:	+44 (0)1722 892735
Email:	IRASSponsor@uclan.ac.uk

Chief-Investigator (CI)

Name:	Dr Lois Thomas
Address:	School of Health Sciences, University of Central Lancashire, Preston, PR1 2HE
Telephone:	+44 (0)1772 873643
E-mail:	lhthomas@uclan.ac.uk

Trial Office

Address:	Brook Building room 423 University of Central Lancashire Preston PR1 2HE
Telephone:	+44 (0)1772 893713
Fax:	
E-mail:	ICONSLCTU@uclan.ac.uk
Website:	http://www.uclan.ac.uk/research/explore/groups/ctu.php

Funder

Name:	NIHR Health Technology Assessment
Funder number:	HTA Project: 16/111/31
Funder start date:	1st May 2018
Funder end date:	31st January 2021

Other

ISRCTN number	ISRCTN14005026
IRAS number:	IRAS Project ID 235402
REC number:	

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above trial.

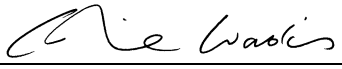
[Insert name of CI]: Dr Lois Thomas

Date: 30/08/2019

[Insert name of Statistician]: Dr Svetlana Tishkovskaya

Date: 30/08/2019

[On behalf of Lancashire Clinical Trials Unit]:



Date: 30/08/2019

VERSION HISTORY

Amendment no.	Protocol version no.	Description of changes (*incl. author(s) of changes*)	Date of protocol
MA 06	2.1	From Version 2.0 04/06/2018 to Version 2.1 30/08/2019. All changes made by Denise Forshaw	30/08/2019
MA 06	2.1	Feedback from sites is that there is a large number of patients that are too ill within the inclusion 72 hour conscious level criteria but that a number of these do improve and could potentially benefit from the opportunity to participate in this study. Therefore we have amended the time frame for inclusion to allow patients (or their consultee) who improve/stabilise within the first 14 days of admission to be considered and approached. This does not in any way change the intervention nor any study activities but rather widens the scope for eligible patients to participate. Addition of comment for Inclusion criteria under 'Section 4.2; Trial Population; Inclusion criteria: FROM: - conscious: "Alert" or "Not alert but arousable" (NIHSS Point 1A score 0-1) on the NIH Stroke Scale (2, 3) within 72 hours of admission to the stroke unit TO: - conscious: "Alert" or "Not alert but arousable" (NIHSS Point 1A score 0-1) on the NIH Stroke Scale (2, 3) within 14 days of admission to the stroke unit. N.B. Patients must be recruited within 72 hours of meeting this criteria wherever possible	30/08/2019
MA 06	2.1	Addition of comment for Inclusion criteria under 'Section 4.3 Identifying and approaching participants: FROM: Patients meeting the inclusion criteria will be recruited within 72 hours of admission to the stroke unit TO: Wherever possible patients meeting the inclusion criteria will be recruited within 72 hours of admission to the stroke unit There will be some patients who will be too ill in this period but may improve, therefore for these patients the recruitment window will be up to 14 days post admission. Recruitment should always be within 72 hours of meeting the inclusion criteria for all patients wherever possible.	30/08/2019

TABLE OF CONTENTS

PROTOCOL SUMMARY

Question addressed	Is a systematic voiding programme a clinically effective and cost effective treatment for urinary incontinence (UI) in patients with urinary incontinence after stroke in secondary care?
Considered for entry	Men and women admitted to a hospital stroke unit with stroke and urinary incontinence, including those with cognitive impairment.
Inclusion/Exclusion criteria	***Inclusion criteria:*** adult patients with: i. acute stroke ii. UI (at least one episode within 72 hours) OR an indwelling urinary catheter iii. NIH Stroke Scale level of consciousness 0-1 ***Exclusion criteria:*** i. long-term indwelling urinary catheter pre-stroke ii. subdural or subarachnoid haemorrhage
Interventions	1. Systematic voiding programme and protocol for indwelling urinary catheter removal PLUS Usual Care 2. Usual Care
Outcomes	Severity of UI Urinary symptoms Number of urinary tract infections Number of days indwelling urinary catheter in situ Functional independence Quality of life Falls Death Cost
Co-ordination	**Local**: by local lead Principal Investigator **Central**: by Lancashire Clinical Trials Unit in Preston (Telephone +44 (0)1772 893713). **Overall**: by the Trial Management Group and overseen by the Trial Steering Committee and the Data Monitoring and Ethics Committee.

GLOSSARY OF ABBREVIATIONS	
AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
GP	General Practitioner
HTA	Health Technology Assessment
ICIQ-UI-SF	International Consultation on Incontinence Questionnaire
ISRCTN	International Standard Randomised Controlled Trial Number
IQoL	Incontinence Quality of Life instrument
LUSQ	Leicester Urinary Symptoms Questionnaire
MCA	Mental Capacity Act 2005
NHS	National Health Service
NIHR	National Institute for Health Research
OG	Operational Group
PI	Principal Investigator
PCPI	Patient, Carer and Public Involvement
PIL	Patient Information Leaflet
TMG	Trial Management Group
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCLan	University of Central Lancashire
UK	United Kingdom
UI	Urinary Incontinence

TRIAL PERSONNEL

Chief Investigator

1 Dr Lois Thomas

Grant Holders

1	Professor Christine Roffe	9	Dr David Britt
2	Professor Joanne Booth	10	Mr Cliff Panton
3	Professor Christopher Chapple	11	Dr Kina Bennett
4	Professor Dame Caroline Watkins	12	
5	Professor Brenda Roe	13	
6	Dr Christopher Sutton	14	
7	Professor Bruce Hollingsworth	15	
8	Dr Ceu Mateus	16	

Trial Office Team - at the University of Central Lancashire

1	Principal Trial Manager	Mrs Denise Forshaw
2	Trial Manager	Emma Neil

Trial Statisticians

1	Trial Statistician (blinded)	Dr Svetlana Tishkovskaya
2	Trial Statistician (unblinded)	Dr Christopher Sutton

Trial Management Group (TMG)

This Group is comprised of all grant holders along with representatives from the Trial Office team.

Trial Steering Committee (TSC) Members

The membership of this Committee comprises independent members along with the Chief Investigator (Lois Thomas). The other ICONS II grant-holders and key members of the Trial Office team (e.g. the Principal Trial Manager and Trial Statisticians) will normally attend TSC meetings. The funders and sponsor will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate.

Independent TSC members:

1	Professor Kate Seers, University of Warwick (Chair)
2	Professor Pip Logan, University of Nottingham
3	Professor Christopher Burton, Bangor University
4	Dr Christopher Price, Newcastle University
5	Mrs Denise Button, Royal United Hospitals Bath NHS Foundation Trust
6	Dr Jonathan Hewitt, Cardiff University
7	Ms Alison Allam, independent PCPI member
8	Dr Manuel Gomes, UCL
9	Dr Marta Soares, University of York
10	Dr Philip Bell, independent PCPI member

Data Monitoring Committee (DMEC) Members
This Committee comprises independent members, with the blinded and unblinded trial statisticians contributing as appropriate. The CI and/or a delegate may contribute to the open session of the meetings as appropriate.

1	Professor Martin Dennis (Chair), Edinburgh University
2	Professor Peter Langhorne, University of Glasgow
3	Dr Munya Dimairo, University of Sheffield

1. INTRODUCTION

1.1 Background

This study addresses the management of urinary incontinence (UI) in patients admitted to hospital with acute stroke. UI affects around half of stroke survivors in the acute phase (4-6). As many as 44% and 38% of stroke survivors remain incontinent at 3 months and 1 year respectively (7). UI often presents as a new problem after stroke or, if pre-existing, worsens significantly, adding to the disability and helplessness caused by neurological deficits (8).

The more severe the stroke, the greater the likelihood of UI (9, 10); other factors include older age or cognitive impairment (11). Urge incontinence (involuntary leakage immediately following, or concurrent with, an urgent sensation of needing to void (12)) is the most common type after stroke (13) and is generally the result of detrusor over-activity (14).

It is important to study UI in this population as symptoms are more severe and have more of an effect compared with other groups of people (8). Furthermore, associated stroke impairments compound difficulties with bladder control with motor, visual or speech problems making the task of accessing toilet facilities a challenge (15).

UI is distressing for individuals and families and depression is twice as common in stroke survivors who are incontinent (16). Negative social consequences for survivors and carers cannot be ignored: both may become isolated and marginalised (17). Continuing incontinence is associated with poor outcome in both stroke survivors and carers (5, 6, 18).

Despite clinical guidelines stating IUCs should only be used to relieve retention (19) there is over-reliance on catheterisation as a management strategy for UI in stroke units, especially in the acute phase (20, 21). This puts patients at risk of IUC-associated urinary tract infection and its consequences (22-25), including increased morbidity, mortality and resource use (23, 26, 27). In ICONS, 48% of patients in intervention arms were catheterised in the acute phase (28). Urinary tract infection and antibiotic use are considerably higher in patients with IUCs, with increasing risk of infection associated with later removal (29). ICONS II promotes catheter avoidance and is likely to reduce the need for antibiotic treatment.

We expect our intervention to reduce the number of patients with UI by at least 5% and improve continence in at least a further 5-10%. If shown to be effective and adopted across the UK, assuming 40,000 stroke survivors per annum have UI at 3 months (7), around 2000 patients would become continent and around 2000-4000 would have improved continence. Currently, patients with UI after stroke typically receive care focused on containment using strategies that do not promote continence (e.g. pads) and are likely to be harmful (e.g. IUCs (20, 21, 28)). The ICONS II trial will provide high quality evidence regarding the clinical and economic effects of a new paradigm for UI after stroke.

1.2 Rationale for the trial

Stroke is the third largest cause of death and the largest single cause of severe adult disability (30), with up to 95,000 people per annum surviving a stroke in the UK. Incidence of stroke is unlikely to decline given the ageing population (31), and prevalence continues to rise (32, 33). Stroke patients with UI have considerably worse outcomes: there is a clear association between UI after stroke and death, disability and an increased likelihood of being discharged into residential care (5, 9, 34). Addressing UI early and effectively could have a major impact on these outcomes and significantly improve quality of life for patients (35).

Improving the management of UI after stroke has been identified as an urgent priority in successive Sentinel Stroke National Audit Programme (SSNAP) reports (36, 37) but there is little evidence this

aspect of care has improved. Consequently, NICE have recommended further research into improved continence care after neurological events (38).

This trial is the first to test the effect of a programme to assess and treat UI after stroke in hospital, building on our feasibility trial (28, 39, 40). While the feasibility trial was not powered to demonstrate effectiveness, there are indications the intervention may work, particularly for urge incontinence. Staff believed the programme improved patient outcome and was sustainable: 5 out of 8 sites continued core aspects after the research was completed.

The update of our Cochrane review 'Treatment of urinary incontinence after stroke in adults' has revealed several new studies (41-45), although the conclusion, that data from the available trials are insufficient to guide continence care, is unlikely to change without a definitive trial. ICONS II will address this clear gap in the evidence base.

2. TRIAL AIM AND OBJECTIVES

Aim: The aim of the research is to evaluate the clinical and economic effect of a systematic voiding programme for urinary incontinence (UI) after stroke in secondary care.

Objectives:
INTERNAL PILOT TRIAL:

1. Assess the feasibility of participant recruitment and the success of strategies for minimising contamination (defined as providing all three key aspects of the systematic voiding programme to usual care patients and ICONS II staff providing toileting assistance to usual care patients).

MAIN TRIAL:

2. PRIMARY OBJECTIVE:

Determine if a systematic voiding programme affects:

- severity of UI

compared to usual care.

3. Determine if a systematic voiding programme affects:

- number of urinary tract infections
- number of days indwelling urinary catheter in situ
- urinary symptoms, quality of life, functional independence, falls and mortality

compared to usual care

4. Determine if the systematic voiding programme is cost-effective in terms of quality adjusted life years (QALYs) gained compared with usual care at 6 months post-randomisation.
5. Assess fidelity to the intervention and usual care in a process evaluation.

3. TRIAL DESIGN

The research comprises:

1. A pragmatic, multicentre, randomised parallel group trial to compare the effectiveness of the systematic voiding programme (n=512) with usual care (n=512) in reducing the severity of UI in patients with stroke and UI in secondary care. Results from an internal pilot with a target of 355 participants will determine progression to full trial.

2. A mixed methods process evaluation investigating fidelity to the intervention and usual care.

3. Economic evaluation of the systematic voiding programme compared with usual care.

3.1 Intervention being evaluated

INTERVENTION

The intervention, a systematic voiding programme, was informed by the findings of our evidence syntheses conducted for the PGfAR (28), including barriers and enablers to successful implementation of behavioural interventions for UI (46), in line with the MRC Framework for developing and evaluating complex interventions (47, 48). It was revised following the ICONS feasibility trial.

The systematic voiding programme comprises assessment, behavioural interventions (bladder training or prompted voiding) and review. Assessment includes evaluation of the need for an IUC (to minimise inappropriate catheterisation), a protocol for IUC removal (if clinically justifiable (49)), a 3 day bladder diary (to assess the pattern of UI)(50) and an evidence-based continence assessment (to classify type of UI)(28). The continence assessment includes: history taking, urine dipstick examination and (if indicated) a mid-stream urine specimen tested by microscopic examination, culture and sensitivities; a bladder scan to estimate post-void residual urine volume; and identification of the type of incontinence (stress UI: any response other than 'never' to the Leicester Urinary Symptom Questionnaire (LUSQ) (51) question "Do you ever leak when you do any of the following?"; urge UI: the response 'most of the time', 'sometimes' or 'occasionally' to the LUSQ question "When you get the urge to pass urine, does any leak before you get to the toilet?"; mixed UI: both stress and urge UI; 'functional' UI (defined as mobility or balance restrictions stopping patients reaching the toilet on time).

The intervention will begin within 24 hours of recruitment and will continue until the patient is discharged from the stroke unit.

Patients who are catheterised will be assessed for a trial without catheter. Patients who are not catheterised and are cognitively able will receive bladder training; those with cognitive impairment OR patients with no control over their bladder will receive prompted voiding. ICONS II staff will make this decision (supported by the project-specific research nurse) based on the following criteria:

> **Prompted voiding**: patients with cognitive impairment at baseline, defined as a score of 8 or more on the Six Item Cognitive Impairment Test (6-CIT (52)); OR patients who have no control over their bladder, defined as answering 'all the time' to the ICIQ-UI-SF question 'how often do you leak urine?'
>
> **Bladder training:** patients with no cognitive impairment at baseline, defined as a score of 0-7 on the 6-CIT, and some control over their bladder, defined as answering 'several times a day', 'about once a day', 'two or three times a week' or 'about once a week or less often' to the ICIQ-UI-SF question 'how often do you leak urine?'

For participants catheterised in the acute stage, staff will be asked to conduct a trial without catheter as early as possible unless there is a valid clinical reason not to do so using a modified version of the HOUDINI protocol (49). Once the catheter is removed, participants will begin assessment as described above.

BLADDER TRAINING aims to help patients regain bladder control and regain continence (53). It comprises:

i) focused education for patients and carers on lower urinary tract dysfunction and the theory and practice of bladder training;
ii) individualised voiding regimens to restore regular, normal voiding patterns by progressively lengthening the time interval between voids;
iii) urge suppression techniques;
iv) patient-held voiding diary, a cognitive intervention designed to promote self-awareness of voiding habits (54, 55).

PROMPTED VOIDING aims to improve bladder control and minimise UI episodes using verbal prompts and positive reinforcement from stroke service staff (56). It comprises:

i) approaching participants according to their individualised regimen (e.g. every two hours during waking hours);
ii) asking if they are currently dry or wet;
iii) prompting them to use the toilet;
iv) offering sensitively constructed feedback for correct reporting of dryness/wetness and successful toileting (57).

In both routes, progress is reviewed weekly by clinical staff with adjustment to the voiding regime or change from prompted voiding to bladder training if the patient's cognitive ability or bladder control improves, or from bladder training to prompted voiding if one or both deteriorate.

Clinical staff will be encouraged to alert community services (including early supported discharge teams) during the discharge process so they can continue the programme post-discharge.

ICONS II TRAINING: Prior to the intervention period, members of the clinical team at each site who would like to be part of the trial will be chosen to act as ICONS II staff and deliver the intervention. We anticipate around 16 nurses, eight qualified and eight healthcare assistants, will be sufficient to enable the duty roster to be organised so at least one ICONS II trained staff member will be available to provide the programme to intervention patients during daytime shifts. We will also train around three physiotherapists and three occupational therapists at each site to continue the programme with intervention patients during therapy sessions.

The ICONS II staff will complete an education programme to improve knowledge of continence issues after stroke and enable them to understand and implement the intervention protocol. The education programme has already been developed by the research team, including our Patient, Carer and Public Involvement groups; it will be updated prior to the intervention phase (months -6 to month -1). Training will be largely web-based to facilitate easy access and flexibility. The online programme has been endorsed by the UK Stroke Forum Education and Training (http://www.stroke-education.org.uk/courses/, reference number QM0056) and includes multiple choice assessment of whether learning outcomes have been met. Additional face-to-face sessions will cover practical aspects of intervention delivery and recording. These sessions will also emphasise the importance of minimising contamination within the trial; ICONS II staff will be encouraged not to discuss the intervention with staff not involved in the trial and, wherever possible, not to treat usual care participants. This approach worked successfully in the AVERT trial (58, 59).

Ongoing identification and training of new ICONS II staff is likely to be necessary to cover staff turnover and absence.

CONTROL (USUAL CARE)

The standard patient care pathway often includes inserting an indwelling urinary catheter in the acute phase (139/289, 48% in the ICONS feasibility trial); there is typically no systematic approach to checking the need for continuing catheterisation or conducting a trial without catheter. The pathway may also include checking for urinary tract infection, containment using absorbent products and some form of toileting schedule for a small number of selected patients; this is unlikely to be based on a continence assessment or tailored to the patients' continence pattern.

Referral for specialist assessment is recommended for persistent incontinence, but this is rarely done for stroke patients.

To determine baseline continence practice, we will conduct a retrospective audit of case notes of 40 patients admitted to each unit in the three-month pre-intervention period. Detailed review will be conducted of patients identified as incontinent. Audit data will be collected by the project-specific research nurse in each site.

3.2 Strategies to monitor fidelity to the intervention

Our assessment of fidelity to the intervention protocol will include the following:

a. Proportion of patients catheterised within 72 hours of admission to the stroke unit; for those catheterised, the proportion of patients undergoing a trial without catheter within 72 hours of catheter insertion.

b. Proportion of patients meeting the criteria for bladder training or prompted voiding initially allocated to the correct regime, based on the following criteria:

> **Prompted voiding**: patients with cognitive impairment at baseline, defined as a score of 8 or more on the 6-CIT; OR patients who had no control over their bladder, defined as answering 'all the time' to the ICIQ-UI Short Form question 'how often do you leak urine?'
>
> **Bladder training:** patients with no cognitive impairment at baseline, defined as a score of 0-7 on the 6-CIT, and some control over their bladder, defined as answering 'several times a day', 'about once a day', 'two or three times a week' or 'about once a week or less often' to the ICIQ-UI Short Form question 'how often do you leak urine'?

c. Percentage of occasions participants receiving bladder training or prompted voiding either self-initiated toileting or were prompted to toilet by ward staff within 30 minutes of the prescribed voiding interval.

d. Percentage of occasions intervention participants receiving bladder training or prompted voiding given toileting assistance from ICONS II staff.

We will review fidelity data **every two weeks** during the first two months of the intervention period to assess whether the intervention is being implemented as per protocol and, if not, to review the need for further training. "Acceptable" is defined as a) removal of IUCs within 72 hours of catheter insertion for 80% of participants with an IUC; b) toileting by ward staff within 30 minutes of the prescribed voiding interval on an average of at least 60% of occasions for at least 80% of participants on bladder training or prompted voiding; and c) provision of toileting assistance by ICONS II staff to at least 90% of intervention patients on at least 60% of occasions.

Lancashire CTU will review site performance against these criteria at the end of every two week period during the first two months of the intervention period and subsequently until fidelity is acceptable. Fidelity will then be reviewed **monthly** for the remainder of the trial intervention period. In sites where fidelity is not acceptable, we will discuss strategies for improving fidelity with the sites involved, and develop and implement a plan for improvement.

Fidelity to usual care will be assessed through our assessment of contamination (described in Section 3.5).

3.3 Methods to protect against contamination

In ICONS II, both intervention and usual care participants are situated on the same unit. We will introduce the following procedures to minimise contamination wherever possible:

- situating intervention and usual care patients in different bays
- staff trained in the ICONS II systematic voiding programme will minimise provision of toileting assistance to usual care participants

Substantial contamination is unlikely as our intervention is complex and aims to change behaviour (60, 61) and the intervention period is expected to be too short for permeation into routine care (62).

To assess contamination of usual care, we will examine a) the extent to which ICONS II staff provide toileting assistance to usual care participants, and b) the extent to which usual care participants receive the intervention (see Section 3.5).

3.4 Relevant concomitant care

Patients in both trial arms may receive bowel care for urinary retention, pharmacotherapy for bladder dysfunction, for example antimuscarinic drugs or mirabegron for overactive bladder symptoms, and/or alpha blockers or finasteride for symptoms associated with an enlarged prostate gland, and/or vaginal oestrogen for atrophic vaginitis. Patients with persistent incontinence may be referred for specialist assessment.

3.5 Internal pilot study

An internal pilot will examine **feasibility of participant recruitment** and the **success of strategies for minimising contamination** (defined as providing all three key aspects of the systematic voiding programme to usual care participants and ICONS II staff providing toileting assistance to usual care participants). We propose clear progression criteria for each below; these will be reviewed and finalised by the TSC in Month -3 (February 2018). A decision about continuing the trial will be taken at Month 10 based on data collected up to the end of Month 8. At this point, sites will have been recruiting participants for 6, 4 and 2 months respectively in Waves 1, 2 and 3.

Recruitment: As site start-up will be staggered with sites beginning in three waves at two-monthly intervals (6 sites in each wave), recruitment data from the first, second and third wave (6 month, 4 month and 2 month recruitment periods respectively – a total of 72 site months of recruitment) will be included in the continuation decision.

Our target is approximately 5 patients per site per month, with an overall target of 355 participants by the end of Month 8. We will assess the success of recruitment in the internal pilot using Thabane et al.'s potential outcomes (63):

Continue: possible to recruit to time and target: recruitment at least 80% of target (minimum 284 participants). If recruitment is at least 80% but less than 100% at this stage, we will consider modifications to the recruitment procedure to ensure our target for the trial as a whole is met.

Continue but modify protocol: may be possible to recruit to time and target with implementation of contingency plans (e.g. increased number of sites): recruitment at least 60% but less than 80% of target (213-283 participants).

Pause trial: may not be possible to recruit to time and target: recruitment less than 60% of target (212 participants or less).

We will review recruitment in each site on a **monthly** basis, both in the internal pilot and the main trial, to enable us to identify and address any issues as they arise.

Contamination monitoring

To assess contamination of usual care, we will examine A) the extent to which ICONS II staff provide toileting assistance to usual care participants, and B) the extent to which usual care participants receive the intervention.

A) Extent to which ICONS II staff provide toileting assistance to usual care participants:

Stroke unit staff will be asked to record brief details of toileting assistance (including the signatures of staff providing assistance) for patients receiving usual care. This will enable us to monitor whether and how often ICONS II staff have delivered toileting assistance to usual care patients.

Outcomes are:

Continue without modification: no more than 25% of usual care participants receive toileting assistance from ICONS II staff on 50% or more occasions.

Continue with modification: more than 25% of usual care participants receive toileting assistance from ICONS II staff on 50% or more occasions.

B) Extent to which usual care participants receive the intervention:

We will conduct a review of case notes for all usual care participants at discharge, focussing on the three key elements of the programme:

i) presence of a strategy for minimising indwelling urinary catheterisation in the acute phase unless clinically justifiable (to relieve urinary retention or when fluid balance is critical (19)). If clinically justifiable, presence of a strategy for review and removal (including trial without catheter).

ii) presence of a comprehensive continence assessment (including continence history, diagnosis of UI [urge/stress/mixed/other], pattern of UI and assessment of relevant co-morbid conditions).

iii) presence of a tailored treatment plan including behavioural approaches (specifically a tailored voiding interval and evidence of review and adjustment).

Some usual care patients will not be discharged at the time point where contamination data are analysed for the internal pilot and their case notes and toileting assistance chart review will therefore not have taken place. To maximise the data available, and to identify site-specific issues, we will conduct an interim review of case notes and charts for all usual care patients not discharged by the end of Month 8. We will continue to monitor contamination for all usual care patients at discharge for the duration of the trial.

Outcomes are:

Continue without modification: 75% or more usual care participants **do not** receive all three key elements of the intervention (avoidance of indwelling urinary catheterisation, comprehensive continence assessment and a tailored treatment plan).

Pause trial: more than 25% of usual care participants receive all three key elements of the intervention.

To determine baseline continence practice, we will conduct a retrospective review of case notes of 40 patients admitted to each unit in the 3-month pre-intervention period. Where possible this will be consecutive to reduce bias. Detailed review will be conducted of patients identified as incontinent. Data will be collected in a format to avoid identification (age in years not date of birth). The case note review will focus on the three elements described above.

Trial continuation decision

Findings will be reviewed by the TSC and DMEC at 10 months. The trial will continue if the outcome for *recruitment* is either **continue** or **continue but modify protocol** and, if the latter, appropriate strategies can be identified to overcome recruitment issues within an appropriate timeframe; **and** the outcome for *contamination: extent to which usual care participants receive the intervention* is **continue without modification**.

If the outcome for *contamination: extent to which usual care participants receive the intervention* is **Continue with modification**, we will investigate reasons and discuss these with the Trial Steering Committee and Trial Management Group. Potential solutions might include: retraining ICONS II staff, emphasising the importance of staff "buying into" the purpose of the research, i.e. to find a definitive answer about effectiveness by delivering care to intervention patients as per protocol, and minimising provision of toileting assistance by ICONS II staff to usual care patients; or considering closing a site or sites unable to manage staff rosters to avoid cross-over of staff.

If the outcome for *recruitment* and *contamination: extent to which usual care participants receive the intervention* is **pause trial**, we will discuss options with the TSC, DMEC, funder and sponsor, for example opening new sites if particular sites are performing poorly on one or both measures.

4. TRIAL SETTING AND RECRUITMENT

4.1 Trial setting

The trial will take place in 18 NHS stroke services with stroke units.

4.2 Trial Population

Men and women with stroke and UI, including those with cognitive impairment.

Inclusion criteria:

- adults with acute stroke (64)

- UI defined as "involuntary loss of urine" (1) within 72 hours of admission to the stroke unit or presence of IUC at the time of consent

- conscious: "Alert" or "Not alert but arousable" (NIHSS Point 1A score 0-1) on the NIH Stroke Scale (2, 3) within 14 days of admission to the stroke unit. N.B. Patients must be recruited within 72 hours of meeting this criteria wherever possible

Exclusion criteria:

- long-term indwelling urinary catheter pre-stroke

- subdural or subarachnoid haemorrhage

4.3 Identifying and approaching participants

All patients admitted to participating stroke units will be screened to determine eligibility by clinical research network nurses and project-specific research nurses (one 0.5 WTE research nurse per site). Our aim is to identify all eligible patients to limit the potential for recruitment bias; to facilitate this we will maintain a screening log in each site. Only anonymised data will be retained from patients who are ineligble or do not proceed to participate (age in years, gender, presence/absence of urinary incontinence, presence/absence of indwelling urinary catheter, confirmed stroke). We will use vignettes describing potentially eligible and ineligible patients as part of our training of staff recruiting patients (65). To identify eligible patients, project-specific and clinical research network research nurses will check the case notes and fluid balance charts for all patients admitted to the stroke unit daily to establish presence of urinary incontinence, apart from patients with an indwelling urinary catheter who will be eligible for inclusion if they meet the other inclusion criteria. Study information will be provided to all potentially eligible patients as soon as possible after admission to the stroke unit, i.e. as soon as they experience an incontinent episode or have an indwelling urinary catheter. Wherever possible patients meeting the inclusion criteria will be recruited within 72 hours of admission to the stroke unit There will be some patients who will be too ill in this period but may improve, therefore for these patients the recruitment window will be up to 14 days post admission. Recruitment should always be within 72 hours of meeting the inclusion criteria for all patients wherever possible.

Potential patients who do not speak English will be invited to take part in the study if they have a family member or friend able to interpret for them.

Informed consent for participation in the study will be sought from all patients with the capacity to consent. Our Speakeasy PCPI group developed aphasia-friendly Patient Information Leaflets and

consent forms in the ICONS feasibility trial, we will use these in ICONS II for patients with aphasia. We will respect the right of patients to decline participation, or to withdraw from the study at any time.

As the research is "intended to provide knowledge of the causes or treatment of, or of the care of persons affected by, the same or a similar condition" (Mental Capacity Act 2005, Section 31:5a (66)), and part of our programme (prompted voiding) is targeted primarily at patients with cognitive problems, we believe it is appropriate to involve patients who lack capacity to consent by inviting someone close to the patient to act as 'consultees' and provide advice (rather than consent). The consultee will be someone who knows the patient well and is likely to be either a friend or a family member. As our intervention is designed to include participants with communication problems and/or cognitive problems, carers may:

1) act as a 'consultee', giving assent for their relative/friend to take part in the study;
2) act as informants on behalf of participants who are unable to consent or communicate.

Where the clinical research network nurse or project-specific research nurse believes a patient's capacity is in question, they will identify and provide the information to the patient's personal consultee (usually a family member or friend). Where a personal consultee is not available, a nominated consultee will be identified by the study team, in accordance with the MCA (66).

4.4 Informed consent

Procedures to seek and gain informed consent from eligible potential participants will be agreed with the Research Ethics Committee. An application for NHS ethics and R&D approval will be submitted through the Health Research Authority (HRA) in March 2018 to ensure the trial can commence on 1st May 2018. The application will be submitted to a Research Ethics Committee for research involving adults lacking capacity. Ethical approval will also be sought from the University of Central Lancashire **STEMH** (Science, Technology, Engineering, Medicine and Health) Ethics Committee once NHS ethical approval is obtained.

Participant recruitment

All recruitment will be undertaken by the clinical research network nurses and project-specific research nurses. Where the patient lacks capacity to consent, a personal or nominated consultee will provide advice on what they feel the person's wishes would be if they had capacity. The consultee will sign a declaration form if they believe the patient would choose to agree to participate. Consultees may advise at any point that they believe the person's wishes about participation have changed and they should therefore be withdrawn from study participation.

Participants who fulfil the eligibility criteria and have consented and completed their baseline questionnaire will then be randomised to intervention or usual care (see Section 6.3, Allocation).

5. OUTCOME MEASURES

5.1 Primary outcome measure

International Consultation on Incontinence Questionnaire–Urinary Incontinence-Short Form (ICIQ-UI-SF (67)) total score at baseline, discharge from the stroke unit, 3 months (primary endpoint) and 6 months post-randomisation.

5.2 Secondary outcome measures

Number of days with indwelling urinary catheter in situ at discharge from the stroke unit, 3 and 6 months.

Number of urinary tract infections at discharge from the stroke unit, 3 and 6 months. A urinary tract infection is defined as: 1A) Symptoms (fever >37.5C on two occasions, or suprapubic tenderness, or

cosovertebral angle pain, or dysuria) OR 1B) A positive blood / urinary tract pus or tissue culture; AND 2) a positive urine culture; OR - for catheterized patients or if a urine culture is not possible - a dipstick positive for nitrite or white blood cells.

Leicester Urinary Symptom Questionnaire (LUSQ (51), questions “Do you ever leak when you do any of the following?” and “When you get the urge to pass urine, does any leak before you get to the toilet?” only) (51) at baseline, 3 and 6 months.

Barthel Index (68) at baseline, 3 and 6 months.

EuroQol (EQ-5D-5L (69)) at baseline, 3 and 6 months.

Incontinence Quality of Life Instrument (IQoL (70, 71)) at 3 and 6 months.

Falls at discharge, 3 and 6 months. A fall is defined as “any fall requiring a medical/health professional examination such as physical examination, x-ray and/or an intervention such as suturing or surgery”.

Death at 3 and 6 months.

Cost.

5.3 Process evaluation measures

Overall

- Recruitment rate
- Withdrawal
- Non-response rate at 3 months
- Non response rate at 6 months

Intervention arm only

a. Number of days on the programme
b. Number of times indwelling catheter inserted
c. Number of days with an indwelling catheter, and reasons for insertion
d. Number of trials without catheter, and the outcome of these
e. Number of changes of route (and whether from bladder training to prompted voiding, or prompted voiding to bladder training)
f. Number of suspensions (defined as one day or more off the programme), with reasons
g. Presence of urinary catheter within 72 hours of admission to the stroke unit
h. For those catheterised, the proportion of patients undergoing a trial without catheter within 72 hours of catheter insertion
i. Proportion of patients meeting the criteria for bladder training or prompted voiding allocated to the correct regime
j. Percentage of occasions participants receiving bladder training or prompted voiding either self-initiated toileting or were prompted to toilet by ward staff within 30 minutes of the prescribed voiding interval.
k. Percentage of occasions intervention participants receiving bladder training or prompted voiding given toileting assistance from ICONS II staff.

Relevant data for a) to i) will be extracted from the **baseline assessment** and the **log of ongoing continence events** forms by the Trial Office team.

Data for j) and k) will be extracted from **daily clinical logs** (completed daily by clinical staff for all patients on bladder training or prompted voiding) specific to each route for all participants in the intervention group by the Trial Office team.

Control arm only

l. Number of occasions toileted

m. Number of occasions toileted by ICONS II staff

n. Proportion of occasions toileted by ICONS II staff

o. Percentage of participants with:

    i. a strategy for minimising indwelling urinary catheterisation in the acute phase unless clinically justifiable

    ii. Percentage of participants with a comprehensive continence assessment;

    iii. Percentage of participants with a tailored treatment plan (including behavioural approaches);

p. Percentage of participants with i, ii, and iii.

Data for l) to p) will be extracted from fluid balance chart review and case note review at discharge.

6. SAMPLE SIZE AND PROPOSED RECRUITMENT RATE

6.1 Sample size

Three month ICIQ-UI-SF total scores from 818 participants will provide at least 90% power to detect a 1.89 point between-arms difference (72) using an independent-samples t-test (alpha=5%), assuming no more than 25% of the true effect is lost due to contamination (based on a minimally important difference of 2.52 (72)) and a common SD of 8.32 (computed from data collected for the ICONS feasibility trial (28)). If we limit contamination so no more than 20% of the true intervention effect is lost (2.01 point between-arms difference), we will achieve 93% power, or protect against under-estimation of the SD (90% power is maintained providing the SD is no more than 8.88; the upper 1-sided 80% and 90% confidence limits are 8.60 and 8.75). We will randomise 1024 participants to allow for 20% attrition (28, 40).

6.2 Recruitment rates

Site start-up will be staggered with sites beginning in three waves at two-monthly intervals (6 sites in each wave). Our target is approximately 5 patients per site per month. Recruitment will be undertaken over a 16-month period, commencing in month 3 and finishing in month 16.

All trial outcome and process evaluation data will be collected by month 24 (see Gantt chart: Figure 1).

6.3 Allocation

Randomisation (1:1 ratio) will be stratified by baseline continence category (catheterised; slight: ICIQ-UI-SF score 1-5/moderate: 6-12; severe/ very severe: 13-21) using blocks of random length; we found this to be prognostic of outcome in our feasibility trial (28); and site. The allocation procedure will be delivered using the secure remote web-based system provided by Sealed Envelope.

Information required to perform the randomisation will be submitted by the research nurse who has obtained consent; they will be required to confirm that they have checked the eligibility criteria prior to the allocation being made. Information on the allocated group will be provided by Sealed Envelope to the research nurse in each stroke unit. The research nurse will record the allocated group on the participant registration form and inform the stroke unit ICONS II staff who will deliver the allocated intervention.

Blinding of healthcare staff and patients is not possible. Data coordinators at Lancashire CTU will also not be blinded as they will be handling data from the process evaluation in addition to baseline and outcome data. However, the Trial Statistician in Lancashire CTU responsible for the Statistical Analysis Plan and the analysis of the effectiveness data will remain blind to the identity of the group codes until after the effectiveness analysis is performed.

6.4 Administration arrangements post-recruitment (if applicable)

Following recruitment, the following administration arrangements will be undertaken:

- The research nurse will file a copy of the consent form in the patient's case noted along with information about the trial.
- The research nurse will return a copy of the signed consent form to the Trial Office in Preston.
- The research nurse will complete a participant registration form and return this to the Trial Office in Preston.
- The site will notify the patient's GP/medical practitioner in writing that the patient has joined the trial.
- The research nurse will file a copy of the GP/medical practitioner letter in the patient's case notes.
- When the participant is discharged, the research nurse will complete a discharge notification form and a discharge outcome form and return this to the Trial Office in Preston.
- The research nurse will maintain trial documentation at their site.

7. DATA COLLECTION AND PROCESSING

7.1 Measuring outcomes

Table 1 (below) summarises what outcomes are assessed at baseline, discharge from the stroke unit, 3 months and 6 months post-randomisation assessments.

Table 1

	Baseline	**Discharge**	**3 months**	**6 months**	**Data collector**
Number of days urinary catheter in situ since the last assessment	Yes/No	●	●	●	Research nurse Participant
Number of UTIs since the last assessment	Yes/No	●	●	●	Research nurse Participant
ICIQ-UI-SF	●	●	●	●	Research nurse Participant
LUSQ	●		●	●	Research nurse Participant

	Baseline	Discharge	3 months	6 months	Data collector
Barthel Index	●		●	●	Research nurse Participant
IQoL			●	●	Research nurse Participant
EQ-5D-5L	●		●	●	Research nurse Participant
Falls		●	●	●	Research nurse Participant
Death		●	●	●	Research nurse Participant's GP

7.2 Baseline - all participants

The project-specific research nurse will collect the following baseline information following consent and will complete the Case Report Form:

- **Information to be collected from case notes:**
- date of birth (age to be calculated)
- gender
- ethnicity
- date of admission
- date of stroke onset
- NIH Stroke Scale at baseline (2, 3) (Scores closest to the date of baseline questionnaire completion will be used)
- side of body affected by stroke (left, right, neither, both)
- type of stroke (cerebral infarct, cerebral haemorrhage)
- stroke sub-type (Oxford Community Stroke Project classification (73, 74))
- pre-stroke Modified Rankin Scale (mRS (75))
- pre-stroke living circumstances
- pre-stroke UI
- indwelling urinary catheter in situ
- type of UI (urge UI, stress UI, mixed UI, 'functional' UI or unclear)

- **Information to be collected from the participant, consultee or clinical staff**
- date baseline questionnaire completed
- cognitive ability (6 Item Cognitive Impairment Test (52)).
- ICIQ-UI-SF
- LUSQ

- Barthel Index
- EQ-5D-5L

7.3 Follow-up

Discharge from the stroke unit – all participants

The following information will be collected by the project-specific research nurse prior to discharge:

- ICIQ-UI-SF
- Number of days indwelling urinary catheter in situ since admission to the stroke unit
- Number of urinary tract infections since admission to the stroke unit
- Number of falls since the last assessment
- Death

In addition to the above, a case note review of continence care will be undertaken **for usual care participants only**.

3 months post randomisation (Primary outcome point) - all participants:

Questionnaires will be sent by post to the participant or consultee. Postal and telephone reminders will be used if questionnaires are not returned within two weeks of the date of the initial mailing. Where completion of postal questionnaires is not possible, participants (or carers if a proxy was needed) will be invited to complete assessments over the telephone with an interviewer blind to the participants' allocation.

Questionnaires will be checked and participants will receive a follow-up telephone call to clarify input where items are missing, inconsistent or take on extreme values.

If participants do not return their questionnaires within two weeks of the date of the initial mailing, we will contact their GP before any telephone or postal reminders both at three and six months.

The participant or consultee will complete the CRF including:

- ICIQ-UI-SF
- LUSQ
- Barthel Index
- IQoL
- EQ-5D-5L
- Number of falls since the last assessment
- Number of days indwelling urinary catheter in situ since the last assessment
- Number of urinary tract infections since the last assessment

6 months post randomisation – all participants

The procedure described above for 3-month outcome data collection will be used.

The participant or consultee will complete the CRF including:

- ICIQ-UI-SF

- LUSQ
- Barthel Index
- IQoL
- EQ-5D-5L
- Number of falls since the last assessment
- Number of days indwelling urinary catheter in situ since the last assessment
- Number of urinary tract infections since the last assessment

7.4 Capture of data from medical records

Baseline data on medical condition will be recorded from the patients' medical records by the research nurse after obtaining consent to participate, prior to randomisation (see Section 7.2). Data captured will include:

- Biographical information
- Type of stroke
- Continence history
- Current medication

7.5 Collection of resource use data

The economic evaluation will compare the costs and outcomes of the systematic voiding programme compared with usual continence care. The economic analysis will take the perspective of the NHS, Personal Social Services (PSS) and the patient. In-hospital costs will be recorded relating to management of UI. After discharge, resource use data will be collected every month for 6 months post-randomisation and will include direct medical and non-medical costs. The main economic outcome is the quotient between incremental changes in costs per QALYs assessed using the EQ-5D-5L at baseline and 6 months.

Resource use data will be collected in hospital and after discharge. In-hospital data will be recorded about staff input in relation to the management of incontinence. This will include the grade of staff involved and time spent on incontinence-related activities. Data regarding use of equipment and consumables and total length of hospital stay will be recorded, as will: staff time spent in training; toileting patients and cleaning patients following an episode of incontinence; equipment (bladder scanner, commode, slipper pan and hoist); consumables, including bottles, pads, mattresses and personal items, and catheters. After discharge, resource use data will be recorded on direct medical and non-medical costs: readmission to hospital, health care input (e.g. GP contacts), therapy services, social services, aids, adaptations and consumables in relation to incontinence, time spent by carers in incontinence related activities; and indirect costs.

The in-hospital resource use data will be based on staff observation over a two day period at each site. These observation periods will be used to make estimates of the in-hospital costs. At each site, staff will be observed by a research associate and data will be recorded around the input needed to manage incontinence in terms of staff time, equipment and consumables, as described previously. Observations will be overt and the purpose (to inform the analysis of a research project) made explicit. The research associate will sit at the door of the bay and take note of the materials staff take when they go to the patient's bed to provide care. Time spent providing care will be noted. When the member of staff leaves the bay, the list of materials will be checked again to record what has been used. The patients' privacy will be maintained at all times. As in our feasibility trial we will estimate costs of incontinence for four groups of patients based on their level of dependence using the transfer item in the Barthel Index. The observation period will occur once at each site to provide estimates of time for each of the four patient groups: the estimates will then be applied to all patients. Data from all sites will be pooled

to allow estimates of the in-hospital costs of incontinence and the intervention. Costs after discharge from hospital will be recorded by a mixture of questionnaires and interviews.

Questionnaires: Patients will be asked to complete a questionnaire every month for six months to record information concerning the use of: therapy services, GP contacts, aids and adaptations, social services, consumables in relation to incontinence, time spent by carers in incontinence-related activities, personal purchases of equipment. We will also record readmission to hospital. Patients will be given the option of receiving all six questionnaires at discharge, or receiving them through the post every month for six months after discharge. Questionnaires will be checked and a follow-up telephone **interview** will be performed to clarify input where items are missing, inconsistent or take on extreme values.

Quality of Life

Participant quality of life data will be collected as described in Sections 7.2 and 7.3 on Outcomes.

7.6 Change of Status/Withdrawal procedures

Participants will remain in the trial unless they or their personal or nominated consultee advises that they believe the person's wishes about participation have changed, they are unable to continue for a clinical reason, or if they die. All changes in status, with the exception of complete withdrawal of consent, mean the participant will still be followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal will be retained and used in the analysis.

If participants withdraw from the intervention, they (or their consultee) will be asked to consider if they wish (the patient) to remain in the trial and be followed up as per trial schedule. This information will be recorded by the research nurse on the Participant withdrawal form.

7.7 Data management

Paper based and electronic data entry will be used. Wherever possible, research nurses will enter locally collected data in the stroke units for screening and randomisation purposes. Where data entry at the site is not possible, paper based data will be transferred to the Lancashire Clinical Trials Unit using SOHO66, an electronic encryption service acceptable to the NHS.

Paper based CRF data will be delivered securely to the Trial Office or, in the case of follow-up data from discharged patients, by Royal Mail following participant (or consultee) self-completion, for data entry.

Questionnaires will be checked and participants will receive a follow-up telephone call to clarify input where items are missing, inconsistent or take on extreme values.

All data will be entered at the Trial Office. Staff in the Trial Office will work closely with local PIs and research nurses to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

A Data Management Plan will be developed containing full details of CTU data monitoring processes.

8. MONITORING

8.1 Data Monitoring

The DMEC will provide an advisory role, assessing the safety of the intervention during the trial and monitoring the overall conduct. The Committee will review confidential interim analyses of accumulating data. The DMEC will also advise on progression based on findings from the internal pilot.

ICONS II has adapted the DAMOCLES Charter for DMECs (76).

8.2 Harms

Standard definitions

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE is considered for severity, causality or expectedness and may be reclassified as a serious adverse event based on prevailing circumstances.

A **serious adverse event** (SAE), is any AE, that:

- results in death;
- is life threatening (i.e. 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 hospitalisation;
- results in persistent or significant disability or incapacity;
- is otherwise considered medically significant by the investigator.

8.3 Trial specific considerations

In this trial, all AEs potentially related to the treatment will be recorded for both intervention and usual care participants (see definitions below). Given findings from the feasibility trial, serious related AEs are not anticipated and this trial can be considered low-risk. However, any serious related AEs that do occur will be recorded as such.

Hospitalisations for elective treatment of a pre-existing condition are not considered as an AE or SAE. Complications occurring during such hospitalisation are also not AEs or SAEs.

ICONS II specific treatment-related expected adverse events:

In this trial the following related AEs are potentially expected:

1. Urinary tract infections
2. Falls requiring medical attention. Falls will be considered as a related AE/SAE only if they occur during continence-related activities.

The following AEs and SAEs are expected within the patient study population **following discharge from the stroke unit** and will be established at 3 and 6-month follow-up.

- Death
- Hospital admissions and re-admissions for any reason
- Institutionalisation
- Treatment on an emergency outpatient basis

As these events are expected within the study population following discharge from the stroke unit they will not be subject to expedited reporting to the main REC. They will however, be included in the annual safety report provided to the main REC.

8.4 Procedures for detecting, recording, evaluating and reporting AEs and SAEs

8.4.1 Detecting AEs and SAEs

All AEs and SAEs meeting the criteria for recording within the ICONS II trial (see section 8.3) will be recorded from the time a participant consents to join the trial until the final trial follow-up. This information will be collected as part of outcome assessment at 3 and 6 months post-randomisation.

8.4.2 Recording AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the PI to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Principal Investigator (PI) should then record all relevant information in the Adverse Event Form or on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes type of event, onset date, PI assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

8.4.3 Evaluating AEs and SAEs

Seriousness, relatedness (causality), and expectedness will be evaluated by a registered healthcare professional.

Assessment of Seriousness

The local PI will make an assessment of seriousness as defined above.

Assessment of Relatedness (causality)

The local PI will make an assessment of whether the AE is likely to be related to research procedures according to the following definitions:

- **Related**: resulted from the systematic voiding programme.
- **Unrelated**: where an event is not considered to have resulted from the systematic voiding programme.

Alternative causes such as natural history of any underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment will be considered.

Assessment of Expectedness

When assessing expectedness, expected events will be referred to (Section 7.2).

8.4.4 Notification and reporting AEs and SAEs

Once the local PI or locally designated health professional becomes aware that an SAE has occurred in a study participant, they will report the information to the Lancashire CTU office within 24 hours. The SAE form will be completed as thoroughly as possible with all available details of the event and signed by the PI. If the local PI does not have all information regarding an SAE, they will not wait for this additional information before notifying the Lancashire CTU office. The form will be updated when the additional information is received.

The SAE form should be transmitted by fax/email to the Lancashire CTU Office.

Reporting responsibilities of the local PI and CI

If, in the opinion of the local PI and the CI, the event is confirmed as being related and unexpected, the CI will submit a report to the main REC, and the DMEC within 15 days of the CI becoming aware of it.

Collaborators and participants may contact the Chair of the TSC through the Lancashire CTU office about any concerns they may have about the trial. If concerns arise about procedures, participants or clinical or research staff (including risks to staff) these will be relayed to the Chair of the DMEC.

8.4.5 Regulatory reporting requirements

The CI will be responsible for submitting annual reports to the REC on the anniversary of the approval. All related SAEs will be summarised and reported to the Ethics Committee, the Funder, the Trial Steering Committee and the Data Monitoring and Ethics Committee in their regular reports.

8.4.6 Follow-up procedures

Follow up procedures

After initially recording an AE or recording and reporting an SAE, the local PI will follow each participant's medical progress. Follow up information on an SAE should be reported to the Lancashire CTU office when received.

Auditing Trial Conduct

The trial is monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of GCP, and all other appropriate regulations. The ICONS II monitoring plan includes adherence to the Protocol Adherence Checklist which will be assessed during site monitoring visits undertaken by members of the Trial Office. Investigators and their host institutions are required to permit trial-related monitoring and audits to take place by the Sponsor and/or regulatory representatives, providing direct access to source data and documents as requested.

9. STATISTICAL ANALYSIS

A Statistical Analysis Plan (SAP) based on the intention-to-treat principle will be developed by the CTU statistics team to cover Sections 9.1 to 9.3 below according to Lancashire CTU Standard Operating Procedures (SOPs). The SAP will be ratified by the TSC prior to the first unblinded analysis (at the end of the internal pilot). Any subsequent amendments to the SAP will be exceptional and will be processed in line with Lancashire CTU SOPs.

9.1 Main effectiveness analysis:

Analysis of the effectiveness outcomes will be 'as randomised'; for the primary incontinence outcome (ICIQ-UI-SF total score), the poorest outcome will be imputed for those catheterised at follow-up. Analysis of incontinence severity will be via linear modelling, including the stratification factor (baseline continence category and site) and intervention group as covariates. Sensitivity analysis will be performed using alternative analysis sets, including 'as treated', and, unless the percentage of missing data is low (<10%) in both arms, methods for handling missing data under a range of plausible assumptions, informed by an analysis of patterns of non-response. Generalised linear models (logistic regression for dichotomous data, ordinal logistic regression for ordinal data and ANOVA-based models for interval data) will be used for the analysis of the secondary outcomes.

For secondary continence outcomes (LUSQ, IQoL), the poorest outcome will be imputed for those catheterised at follow-up. No imputation for the remaining secondary outcomes will be performed, although sensitivity analysis will consider imputation as appropriate (further details will be included in the SAP). Subgroup analysis: initial planned subgroup analyses are detailed in Section 9.2 below and will be confirmed following discussion with the TSC and then included in the Statistical Analysis Plan. Subgroups will be compared for intervention effectiveness by adding interaction terms to the model for the primary outcome.

9.2 Planned subgroup analyses:

Subject to confirmation by the TSC, subgroup analyses will be carried out accordingly by:

- Age
- Gender

- UI severity
- Stroke severity
- Pre-stroke urinary incontinence
- Pre-stroke Modified Rankin Scale score

9.3 Process evaluation

Process evaluation data (see Sections 3.2, 3.3 and 3.5) will be analysed descriptively using frequency (%), mean (SD) or median (IQR) as appropriate.

9.4 Health economic analysis

For all resources we will identify a unit cost of that resource. These costs will be multiplied by the number of units of each resource used: based on the product, a total cost will be calculated for each group and subsequently a mean cost per group calculated. The cost-effectiveness analyses will be based on Quality Adjusted Life Years (QALYs) gained, estimated from the responses to the EQ-5D-5L using the UK tariff value (77), and symptom-free days (calculated as in our feasibility trial **(28)**). Adjustment for baseline utilities will be taken into account. We will combine the cost and outcome data to determine if one group is dominant. Should there be non-dominance, Incremental Cost Effectiveness Ratios for the cost per QALY gained and cost per symptom-free day will be calculated and reported. Univariate and multivariate sensitivity analyses will be performed around these estimates by varying assumptions around key parameters to determine the robustness of the findings.

Uncertainty about the results of economic assessments in clinical trials can be related to sampling uncertainty, uncertainty in parameters such as unit costs and the discount rate, and (when missing data are present) imputation-related uncertainty.

To address sampling uncertainty, we will report variability for within-group estimates of costs and outcomes, between-group differences in costs and outcomes, and the comparison of costs and outcomes. We will report this variability by constructing a confidence interval for the cost-effectiveness ratio or for net monetary benefit, or by constructing an acceptability curve. Additionally, we will quantify the value of eliminating the uncertainty by estimation of the expected value of information.

As for parameter uncertainty, where parameters such as unit costs or the discount rate can heavily influence the results, the impact of changes will be assessed through sensitivity analysis.

With regard to imputed data, bootstrapping the entire imputation and estimation process will be applied.

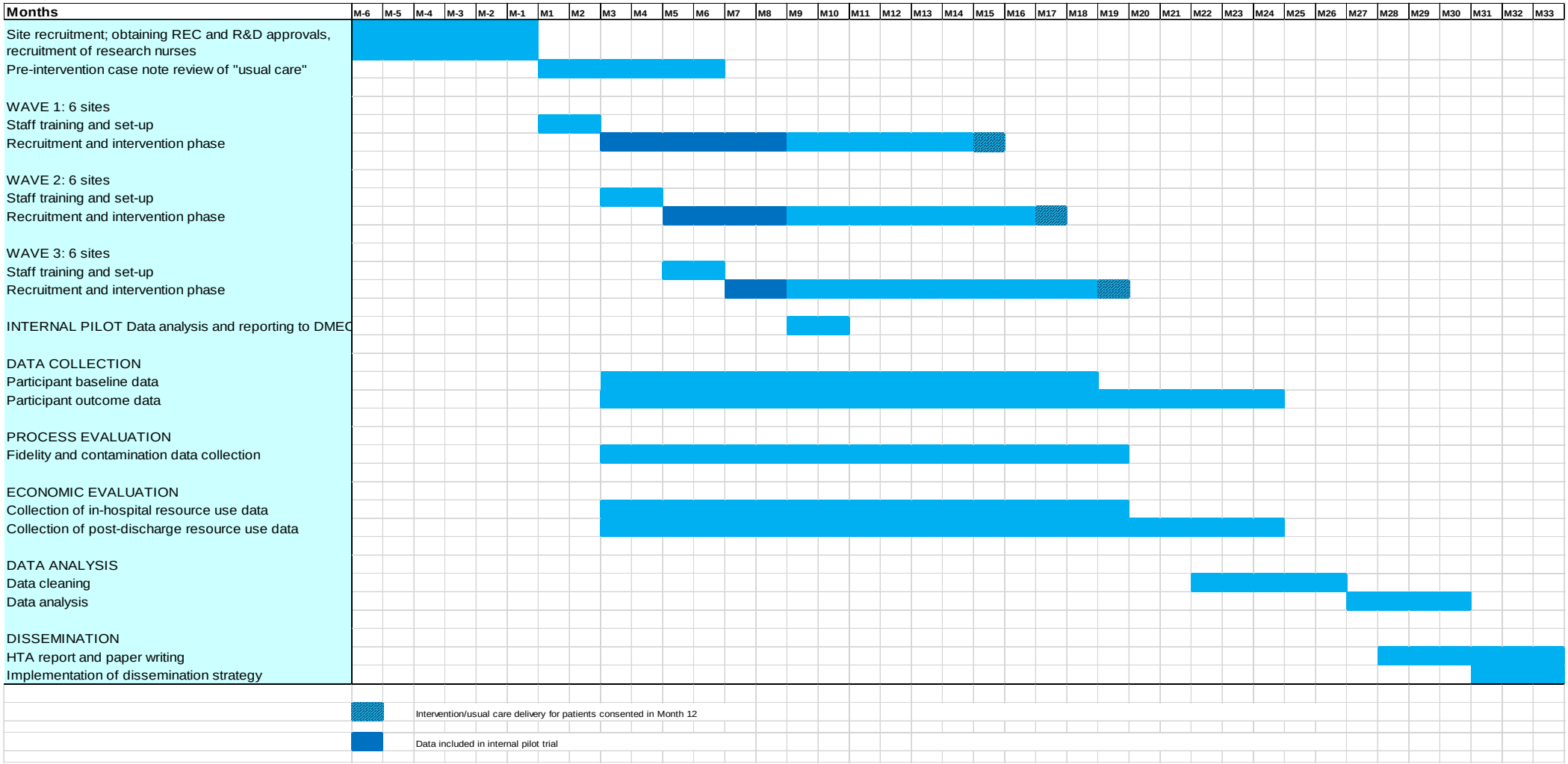
Incomplete cost data will be imputed using multiple imputations. Two cost components will be reported (in-hospital costs; post-hospital costs up to 6 months) and used as the incomplete response variables. The variables likely to be associated with missingness and cost, which will be used to help predict values for missing cost data, will be: age, gender, stroke severity, length of stay, residence, site, trial arm, and survival time.

A Health Economic Analysis Plan will be developed by the health economic team and ratified by the TSC prior to database lock.

10. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

The Gantt chart (Figure 1) indicates when anticipated major trial events will occur, including recruitment and analyses. These time-related milestones will be used to enable close monitoring of progress.

Figure 1 – ICONS II Gantt chart


Months
M-6 M-5 M-4 M-3 M-2 M-1 M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12 M13 M14 M15 M16 M17 M18 M19 M20 M21 M22 M23 M24 M25 M26 M27 M28 M29 M30 M31 M32 M33
Site recruitment; obtaining REC and R&D approvals, recruitment of research nurses
Pre-intervention case note review of "usual care"
WAVE 1: 6 sites
Staff training and set-up
Recruitment and intervention phase
WAVE 2: 6 sites
Staff training and set-up
Recruitment and intervention phase
WAVE 3: 6 sites
Staff training and set-up
Recruitment and intervention phase
INTERNAL PILOT Data analysis and reporting to DMEC
DATA COLLECTION
Participant baseline data
Participant outcome data
PROCESS EVALUATION
Fidelity and contamination data collection
ECONOMIC EVALUATION
Collection of in-hospital resource use data
Collection of post-discharge resource use data
DATA ANALYSIS
Data cleaning
Data analysis
DISSEMINATION
HTA report and paper writing
Implementation of dissemination strategy
Intervention/usual care delivery for patients consented in Month 12
Data included in internal pilot trial

10.1 Lancashire Clinical Trials Unit office

The Lancashire Clinical Trials Unit office is in the Faculty of Health and Wellbeing at the University of Central Lancashire. It will provide day to day support for the trial sites.

The Clinical Trials Manager will take responsibility for day to day trial activities, for example approvals, site set-up and training, oversight of recruitment and monitoring of follow-up rates. The Clinical Trials Manager will be supported and supervised by the Principal Clinical Trials Manager. Organisational and other trial management assistance will be provided by the Trials Management Team.

The Information Systems Team will set up the trial information system and maintain the trial database. The Data Management Team will support development of case report forms, develop the data management plan, manage data processes, run reports and archive data. The Data Management Team will liaise with the Information Systems Team regarding the data requirements, and liaise with the Trial Management Team regarding the completion of the CRFs, obtain outcome data via postal questionnaire or telephone and manage the data entry and cleaning process. The Trial Statistician (ST) will perform statistical analysis.

The Lancashire CTU team and the CI (LT) will meet formally at least monthly during the course of the trial to ensure targets are met and to enable any issues to be identified and addressed early.

10.2 Local organisation in participating stroke units

The local PI and research nurse in each site will be responsible for all aspects of local organisation including identifying potential recruits, consenting, and completing and maintaining appropriate documentation. The Site Agreement documents the full list of responsibilities for sites. Appropriate members of the local team will be knowledgeable about the Protocol and will have appropriate Good Clinical Practice (GCP) training if applicable. A trial-specific delegation log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial. The local team will also be responsible for notifying SAEs to the Trial Office (see Section 7).

10.3 Operational Group (OG)

A core group of staff at UCLan (LT [CI], ST [Statistician, Lancashire CTU], CW [Mentor and Director, Lancashire CTU], trial managers and the data manager and, during the database development period, the Senior IS Developer) will meet **monthly** to review progress against objectives, including monthly monitoring of site recruitment during the intervention phase. Other staff, including the unblinded statistician (CS), will be invited to join as necessary as the trial progresses.

10.4 Trial Management Group (TMG)

The trial is supervised by its Trial Management Group (TMG). This is made up of the grant holders and representatives from Lancashire CTU. The group will meet twice during the set-up period (-6 to -1) and then **every three months** during the trial to review progress and discuss issues arising. Observers will be invited to attend at the discretion of the TMG.

10.5 Trial Steering Committee (TSC)

The TSC will provide overall supervision on behalf of the trial's sponsor and maximise the chance of completing on time. Subject to HTA approval, it will include the following Independent Members: Chair (Professor Kate Seers), experts in stroke research and practice (Dr Christopher Price, Dr Jonathan Hewitt, Professor Christopher Burton and Professor Pip Logan), an independent statistician (Marta Soares) and health economist (Manuel Gomes), and Lead Research Practitioner (Denise Button); it will also include two PCPI members (Alison Allam, Dr Philip Bell), the CI and Trial Manager. It will meet **every six months** and to review results from the internal pilot.

The TSC Charter will document the terms of reference of the TSC, the template for reporting, and the names and contact details of members of the TSC. This Charter will be filed in the Trial Master File (TMF).

10.6 Data Monitoring and Ethics Committee (DMEC)

The DMEC will comprise Professor Martin Dennis (Chair), Professor Peter Langhorne, and an independent statistician (Dr Munya Dimairo). Members will decide on appropriate meeting dates; these are likely to be **at least once per year**.

The DMEC Charter will document the terms of reference of the DMEC and names and contact details. It will be filed in the TMF.

11. RESEARCH GOVERNANCE AND ETHICS

11.1 Research Governance

Lancashire CTU has particular expertise in running multicentre RCTs of complex healthcare interventions; ICONS II will adopt its Standard Operating Procedures (SOPs). The CI will ensure adequate systems are in place for monitoring the quality of the trial and providing appropriate expedited and routine reports to a level appropriate to the risk assessment of the trial.

11.2 Data protection

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. It may be looked at by individuals from the Sponsor organisation or participating sites where it is relevant to the participant taking part in the trial.

Participants will be allocated an individual trial number. Participants' details will be stored on a secure database to comply with the 2018 General Data Protection Regulation. In line with Article 17, "Right to erasure", personal data will not be kept for longer than is required for the purpose for which it has been acquired. The Principal Clinical Trials Manager (in collaboration with the CI) will manage access rights to the data set.

11.3 Sponsorship

The University of Central Lancashire is the sponsor for the trial.

11.4. Ethics and regulatory approvals

Wales Research Ethics Committee 5 has reviewed this trial. The trial will be conducted according to the principles of GCP provided by Research Governance Guidelines. Annual progress reports, end of trial declaration, and a final report will be submitted to the Sponsor and the Research Ethics Committee within the timelines defined in the regulations.

11.4.1 Protocol compliance and amendment

The Investigators will conduct the trial in compliance with the protocol given a favourable opinion by the Research Ethics Committee. Any amendment to the project will be approved by the Sponsor and Funder before application to REC, apart from in the case of immediate safety measures when the REC will be notified as soon as possible. Any deviations from the Protocol will be fully documented using a breach report form.

12 RISK ASSESSMENT

A risk assessment will be carried out by the Trial Management Group. It will be reviewed every three months at scheduled meetings.

13. FINANCE AND INSURANCE

The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme (HTA Project: 16/111/31). The necessary trial insurance is provided by the University of Central Lancashire; NHS indemnity is provided through the lead R&D department.

14. END OF TRIAL

The end of follow-up for each participant is defined as the final data capture on that individual. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the Sponsor and REC within 90 days, or 15 days if the trial is terminated prematurely. If terminated prematurely, the Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved, if appropriate.

A summary report of the trial will be provided to the Sponsor and REC within one year of the end of the trial. An end of trial report will also be provided to the Funder at the end of funding.

15. ARCHIVING

Responsibilities for archiving will be documented in the Sponsor/site agreement. All essential data and documents (electronic and hard copy) will be retained for a period of five years after the close of the trial according to the funder requirements and relevant Sponsor and Lancashire CTU archiving SOPs. This will include consent forms, case report forms and the data key. The data key will be pseudonymised and will be securely stored separately from patient data. Electronic data will be archived by the University of Central Lancashire.

ICONS II anonymised data will be made available via the UCLanData repository, and the Virtual International Stroke Trials Archive (VISTA, http://www.vista.gla.ac.uk/) to enable international prospective meta-analyses.

16. KNOWLEDGE MOBILISATION STRATEGY

16.1 Dissemination

NIHR: Trial findings will be written up in the final report to the NIHR HTA Programme and published in the NIHR HTA Journal.

PATIENT PARTICIPANTS AND WIDER PATIENT, PUBLIC AND CARER NETWORKS: Findings will be disseminated to all patients and carers who participated in the research. Presentation of this information will be discussed with the ICONS II Patient, Carer and Public Involvement (PCPI) Groups and is likely to include a normal and an easy access summary.

The appropriate dissemination strategy for wider patient, public and carer networks will be informed by our ICONS II Patient, Public and Carer Groups. A summary of findings will be posted on the INVOLVE website (http://www.involve.org.uk/) and disseminated through the Patient, Carer and Public Involvement Leads in the 15 UK Clinical Networks. The PCPI strand of the trial will be submitted for publication in *Health Expectations* and members of the ICONS II PCPI Groups will present findings at a national conference (e.g. UK Stroke Forum) and local meetings.

CLINICAL STAFF: Findings will be disseminated to all clinical staff who participated in the research. Clinical staff will be encouraged to cascade findings to the rest of the stroke service team through channels such as multidisciplinary team meetings and staff notice boards.

HEALTH COMMISSIONERS AND DECISION MAKERS: Findings will be shared through participating Trust, Clinical Research and Academic Health Science Networks across the UK. Findings will also be sent to relevant national UK organisations, e.g.: Governments and the NHS in England, Scotland, Wales and Northern Ireland; National Institute for Health and Care Excellence, and Royal Colleges (e.g. Royal College of Nursing, Royal College of Physiotherapists). The summary will also be posted on the websites of the research team members' organisations.

POLICY: Findings will be fed into the next update of the Intercollegiate Stroke Working Party National Clinical Guidelines and the NICE guideline on UI in neurological disease in order to facilitate wide access

to health professionals. We will identify key relevant European Union and international clinical guidelines and submit our findings for consideration.

ACADEMIC COMMUNITY: The trial findings and health economic evaluation papers will be submitted as a pair to a high impact journal, for example *The Lancet* or *Stroke*. Findings will also be submitted to profession-specific journals (e.g. *Physiotherapy, Nursing Times*) to maximise readership. Lead authors and timescales will be agreed by the Trial Management Group and will adhere to the ICMJE criteria for authorship http://www.icmje.org/. Please refer to the Appendix 1 (authorship policy) for full details on authorship.

Findings will be presented at a range of stroke, rehabilitation and incontinence related conferences, for example the European Stroke Conference, UK Stroke Forum, International Continence Society Conference and Association for Continence Advice Conference. Key findings will be shared on relevant social media, including blogs and twitter feeds (e.g. @UCLanHealth, @OfficialNIHR, @NIHRCRN).

16.2 Key outputs

There will be three key outputs of this research:

1. High quality evidence regarding the clinical effectiveness and cost-effectiveness of a systematic voiding programme to improve urinary incontinence after stroke. Such evidence does not currently exist in the UK and findings will enable commissioners and clinicians to make evidence-based decisions about adopting the intervention in similar NHS settings.

2. A multidisciplinary workforce with the knowledge and skills necessary to treat urinary incontinence after stroke in 18 stroke services. If the systematic voiding programme is shown to be effective, clinical staff who implemented the intervention will be encouraged to share experiences and practical suggestions for introducing the programme into practice in their units after the intervention period.

3. We will produce a comprehensive manual for implementing the programme should it prove effective and cost-effective. This will include relevant documentation as well as hints and tips for introducing, monitoring and evaluating the change in practice. The manual will be publicised as outlined in the dissemination strategy and will be available on the trial website. It will also include a link to the ICONS II online training.

17. REFERENCES

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. AmJObstetGynecol. 2002;187(1):116-26.
2. Adams HP, Jr., Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology. 1999;53(1):126-31.
3. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989;20(7):864-70.
4. Lawrence ES, Coshall C, Dundas R, Stewart J, Rudd AG, Howard R, et al. Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. Stroke. 2001;32(6):1279-84.
5. Nakayama H, Jorgensen HS, Pedersen PM, Raaschou HO, Olsen TS. Prevalence and risk factors of incontinence after stroke. The Copenhagen Stroke Study. Stroke. 1997;28(1):58-62.
6. Kolominsky-Rabas PL, Hilz MJ, Neundoerfer B, Heuschmann PU. Impact of urinary incontinence after stroke: results from a prospective population-based stroke register. NeurourolUrodyn. 2003;22(4):322-7.
7. Williams MP, Srikanth V, Bird M, Thrift AG. Urinary symptoms and natural history of urinary continence after first-ever stroke--a longitudinal population-based study. Age Ageing. 2012;41(3):371-6.
8. Brittain KR, Perry SI, Peet SM, Shaw C, Dallosso H, Assassa RP, et al. Prevalence and impact of urinary symptoms among community-dwelling stroke survivors. Stroke. 2000;31(4):886-91.
9. Brittain KR, Peet SM, Castleden CM. Stroke and incontinence. Stroke. 1998;29(2):524-8.
10. Burney TL, Senapati M, Desai S, Choudhary ST, Badlani GH. Acute cerebrovascular accident and lower urinary tract dysfunction: a prospective correlation of the site of brain injury with urodynamic findings. JUrol. 1996;156(5):1748-50.
11. Barrett JA. Bladder and bowel problems after stroke. Reviews in Clinical Gerontology. 2002;12:253-67.
12. Marinkovic SP, Badlani G. Voiding and sexual dysfunction after cerebrovascular accidents. JUrol. 2001;165(2):359-70.
13. Pettersen R, Stien R, Wyller TB. Post-stroke urinary incontinence with impaired awareness of the need to void: clinical and urodynamic features. BJUInt. 2007;99(5):1073-7.
14. Arunabh, Badlani G. Urologic problems in cerebrovascular accidents. Problems in Urology. 1993;1:41-53.
15. Brittain KR, Peet SM, Potter JF, Castleden CM. Prevalence and management of urinary incontinence in stroke survivors. Age Ageing. 1999;28(6):509-11.
16. Brittain KR. Urinary symptoms and depression in stroke survivors. Age & Ageing. 1998;27 (Suppl. 1):116-7.
17. Brittain KR, Shaw C. The social consequences of living with and dealing with incontinence--a carers perspective. SocSciMed. 2007;65(6):1274-83.
18. Pettersen R, Wyller TB. Prognostic significance of micturition disturbances after acute stroke. J Am Geriatr Soc. 2006;54(12):1878-84.

19. Intercollegiate Stroke Working Party. National clinical guideline for stroke. London: Royal College of Physicians; 2016.

20. Cowey E, Smith LN, Booth J, Weir CJ. Urinary catheterization in acute stroke: clinical realities. A mixed methods study. Clin Rehabil. 2012;26(5):470-9.

21. Booth J, Kumlien S, Zang Y, Gustafsson B, Tolson D. Rehabilitation nurses practices in relation to urinary incontinence following stroke: a cross-cultural comparison. JClinNurs. 2009;18(7):1049-58.

22. Poisson SN, Johnston SC, Josephson SA. Urinary tract infections complicating stroke: mechanisms, consequences, and possible solutions. Stroke. 2010;41(4):e180-4.

23. Kwan J, Hand P. Infection after acute stroke is associated with poor short-term outcome. Acta Neurol Scand. 2007;115(5):331-8.

24. Roth EJ, Lovell L, Harvey RL, Heinemann AW, Semik P, Diaz S. Incidence of and risk factors for medical complications during stroke rehabilitation. Stroke. 2001;32(2):523-9.

25. Stott DJ, Falconer A, Miller H, Tilston JC, Langhorne P. Urinary tract infection after stroke. QJM. 2009;102(4):243-9.

26. Aslanyan S, Weir CJ, Diener HC, Kaste M, Lees KR, Committee GIS, et al. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. Eur J Neurol. 2004;11(1):49-53.

27. Roth EJ, Lovell L, Harvey RL, Bode RK, Heinemann AW. Stroke rehabilitation: indwelling urinary catheters, enteral feeding tubes, and tracheostomies are associated with resource use and functional outcomes. Stroke. 2002;33(7):1845-50.

28. Thomas LH, French B, Sutton CJ, Forshaw D, Leathley MJ, Burton CR, et al. ICONS: Identifying Continence OptioNs after Stroke: An evidence synthesis, case study and exploratory cluster randomised controlled trial of the introduction of a systematic voiding programme for patients with urinary incontinence after stroke in secondary care. Programme Grants for Applied Research. 2015;3(1).

29. Griffiths R, Fernandez R. Strategies for the removal of short-term indwelling urethral catheters in adults. Cochrane Database Syst Rev. 2007(2):CD004011.

30. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383(9913):245-54.

31. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet. 2009;374(9696):1196-208.

32. Lee S, Shafe AC, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database. BMJ Open. 2011;1(2):e000269.

33. Wolfe C RA, McKevitt C. Modelling, evaluating and implementing cost effective services to reduce the impact of stroke. Programme Grants for Applied Research. 2014;2(2).

34. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. Stroke. 2000;31(9):2080-6.

35. Barer DH. Continence after stroke: useful predictor or goal of therapy? Age Ageing. 1989;18(3):183-91.

36. Royal College of Physicians. Sentinel Stroke National Audit Programme (SSNAP) Clinical Audit January-March 2016 Public Report. London: Royal College of Physicians; 2016.

37. Intercollegiate Stroke Working Party. National Sentinel Stroke Audit 2010. London: Royal College of Physicians; 2011.

38. National Institute for Health and Care Excellence. Urinary incontinence in neurological disease: management of lower urinary tract dysfunction in neurological disease. Clinical Guideline 148: Methods, evidence and recommendations. London: National Clinical Guideline Centre; 2012.

39. Thomas LH, Watkins CL, French B, Sutton C, Forshaw D, Cheater F, et al. Study protocol: ICONS: Identifying continence options after stroke: A randomised trial. Trials. 2011;12.

40. Thomas LH, Watkins CL, Sutton CJ, Forshaw D, Leathley MJ, French B, et al. Identifying continence options after stroke (ICONS): a cluster randomised controlled feasibility trial. Trials. 2014;15(1):509.

41. Guo ZF, Liu Y, Hu GH, Liu H, Xu YF. Transcutaneous electrical nerve stimulation in the treatment of patients with poststroke urinary incontinence. Clin Interv Aging. 2014;9:851-6.

42. Liu Y, Liu L, Wang X. Electroacupuncture at points Baliao and Huiyang (BL35) for post-stroke detrusor overactivity. Neural Regen Res. 2013;8(18):1663-72.

43. Shin DC, Shin SH, Lee MM, Lee KJ, Song CH. Pelvic floor muscle training for urinary incontinence in female stroke patients: a randomized, controlled and blinded trial. Clinical Rehabilitation. 2016;30(3):259-67.

44. Tibaek S, Gard G, Dehlendorff C, Iversen HK, Biering-Soerensen F, Jensen R. Is Pelvic Floor Muscle Training Effective for Men With Poststroke Lower Urinary Tract Symptoms? A Single-Blinded Randomized, Controlled Trial. Am J Mens Health. 2015.

45. Yun SP, Jung WS, Park SU, Moon SK, Park JM, Ko CN, et al. Effects of moxibustion on the recovery of post-stroke urinary symptoms. Am J Chin Med. 2007;35(6):947-54.

46. French B, Thomas LH, Harrison J, Coupe J, Roe B, Booth J, et al. Client and clinical staff perceptions of barriers to and enablers of the uptake and delivery of behavioural interventions for urinary incontinence: qualitative evidence synthesis. J Adv Nurs. 2017;73(1):21-38.

47. Medical Research Council. Developing and evaluating complex interventions: new guidance. London: Medical Research Council; 2008.

48. Medical Research Council. A framework for the development and evaluation of RCTs for complex interventions to improve health. London: Medical Research Council; 2000.

49. Adams D, Bucior H, Day G, Rimmer J. HOUDINI: make that urinary catheter disappear. Journal of Infection Prevention. 2012;13(2):44-6.

50. Bright E, Cotterill N, Drake M, Abrams P. Developing and Validating the International Consultation on Incontinence Questionnaire Bladder Diary. EurUrol. 2014.

51. Shaw C, Matthews RJ, Perry SI, Williams K, Spiers N, Assassa RP, et al. Validity and reliability of a questionnaire to measure the impact of lower urinary tract symptoms on quality of life: the Leicester Impact Scale. NeurourolUrodyn. 2004;23(3):229-36.

52. Brooke P, Bullock R. Validation of a 6 item cognitive impairment test with a view to primary care usage. Int J Geriatr Psychiatry. 1999;14(11):936-40.

53. Wallace SA, Roe B, Williams K, Palmer M. Bladder training for urinary incontinence in adults. Cochrane Database of Systematic Reviews. 2004(1):CD001308.

54. Subak LL, Quesenberry CP, Posner SF, Cattolica E, Soghikian K. The effect of behavioral therapy on urinary incontinence: a randomized controlled trial.[see comment]. Obstetrics & Gynecology. 2002;100(1):72-8.

55. Lentz G, Plevnik S, Stanton SL. Vaginal cones versus bladder drill for sensory urgency treatment. Proceedings of the International Continence Society (ICS), 24th Annual Meeting1994. p. 35-6.

56. Eustice S, Roe B, Paterson J. Prompted voiding for the management of urinary incontinence in adults. CochraneDatabaseSystRev. 2000(2):CD002113.

57. O'Donnell PD. Behavioral modification for institutionalized individuals with urinary incontinence. Urology. 1998;51(2A:Suppl):Suppl-2.

58. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. Stroke. 2008;39(2):390-6.

59. Cumming TB, Thrift AG, Collier JM, Churilov L, Dewey HM, Donnan GA, et al. Very early mobilization after stroke fast-tracks return to walking: further results from the phase II AVERT randomized controlled trial. Stroke. 2011;42(1):153-8.

60. Howe A, Keogh-Brown M, Miles S, Bachmann M. Expert consensus on contamination in educational trials elicited by a Delphi exercise. Med Educ. 2007;41(2):196-204.

61. Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, et al. Contamination in trials of educational interventions. Health Technol Assess. 2007;11(43):iii, ix-107.

62. Langhorne P, Stott D, Knight A, Bernhardt J, Barer D, Watkins C. Very early rehabilitation or intensive telemetry after stroke: a pilot randomised trial. Cerebrovasc Dis. 2010;29(4):352-60.

63. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol. 2010;10:1.

64. Goldstein M, Barnett HJM, Orgogozo JM, Sartorius N, Symon L, Vereshchagin NV. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and Other Cerebrovascular Disorders. Stroke. 1989;20:1407-31.

65. McColl E HP, Brennand C. Using vignettes to understand variations in patient screening and recruitment. Trials. 2015;16 (Suppl 2):O22.

66. Mental Capacity Act. 2005.

67. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. NeurourolUrodyn. 2004;23(4):322-30.

68. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. IntDisabilStud. 1988;10(2):61-3.

69. The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. . Health Policy. 1990;16(3):199-208.

70. Wagner TH, Patrick DL, Bavendam TG, Martin ML, Buesching DP. Quality of life of persons with urinary incontinence: development of a new measure. Urology. 1996;47(1):67-71.

71. Patrick DL, Martin ML, Bushnell DM, Yalcin I, Wagner TH, Buesching DP. Quality of life of women with urinary incontinence: further development of the incontinence quality of life instrument (I-QOL). Urology. 1999;53(1):71-6.

72. Nystrom E, Sjostrom M, Stenlund H, Samuelsson E. ICIQ symptom and quality of life instruments measure clinically relevant improvements in women with stress urinary incontinence. Neurourol Urodyn. 2015;34(8):747-51.

73. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337(8756):1521-6.

74. Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K, et al. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 1. Methodology, demography and incident cases of first-ever stroke. JNeurolNeurosurgPsychiatry. 1988;51(11):1373-80.

75. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van GJ. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19(5):604-7.

76. Damocles Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet. 2005;365(9460):711-22.

77. Devlin N SK, Feng Y, Mulhern B, van Hout B. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. Research Paper 16/01. 2016;Office of Health Economics Research.

APPENDICES

Appendix 1: AUTHORSHIP POLICY FOR ICONS II STUDY

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria[1]:

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
ii. Drafting the work or revising it critically for important intellectual content; AND
iii. Final approval of the version to be published; AND
iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

2. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals[2,3] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE)[1].

- All contributors must fulfil the criteria detailed in section 1: DEFINING AUTHORSHIP in order to qualify for authorship.
- Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or technical editing, language editing or proof reading the article is insufficient by itself to justify authorship[1]. Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.
- Where possible studies should be published using all the named contributors who qualify for authorship in the byline i.e. Jane Doe, John Doe, John Smith and Ann Other. However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstances, group authorship may be appropriate using bylines similar to "The ICONS II trial team". The article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

a. Determining authorship

Authorship criteria are intended to preserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion numbers (ii) or (iii). Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript[1].

Tentative decisions on authorship should be made as early as possible[3]. These should be justified to, and agreed by, the Trial Management Group. Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

b. Ordering of authors

The following rules may help with the ordering of authors, particularly for publications with individual authorship:

i. The person who has taken the lead in writing may be the first author.
ii. The senior author may wish to be the last named author.
iii. Those who have made a major contribution to analysis or writing (i.e. have done more than commenting in detail on successive drafts) may follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.

iv. All others who fulfil the four authorship criteria described in Section 1: DEFINING AUTHORSHIP may complete the list in alphabetical order of their surnames.

3. ACKNOWLEDGEMENTS

In all published papers, posters etc. the list of authors must end with the term "on behalf of the ICONS II trial team and the ICONS II Patient, Carer and Public Involvement groups". All those in the trial team who do not fulfil the criteria for authorship should then be acknowledged by name in the 'Acknowledgements' section. A full list of trial team members should be obtained from the ICONS II CI. As acknowledgment may imply endorsement by acknowledged individuals of a study's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals[1].

All publications and reports of work arising from the ICONS II trial must adhere to the NIHR branding guidance.

4. DISCLAIMERS

Authors should ensure they include the study funder's disclaimer: refer to the funder's website for details. Other disclaimers may also be required.

5. QUALITY ASSURANCE

Ensuring quality assurance is essential to the good name of the trial group. All reports of work arising from the ICONS II trial, including conference abstracts, should be peer reviewed by the Project Management Group. The Trial Management Group will be responsible for decisions about submission following internal peer review. Submission may be delayed or vetoed if there are serious concerns about scientific quality. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

It is hoped that the adoption and dissemination of this policy will prevent disputes that cannot be resolved by informal discussion. However, any member of the study team with a concern about authorship should discuss it with the Chief Investigator.

References

1. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Developed by members of the ICMJE over the period 2011 to 2013. (www.icmje.org/#authors)
2. Huth EJ (1986). Guidelines on authorship of medical papers. Annals of Internal Medicine, **104**, 269-274.
3. Glass RM (1992). New information for authors and readers. Group authorship, acknowledgements and rejected manuscripts. Journal of the American Medical Association, **268**, 99.

Appendix 2 – ICONS II flow diagram