GIG CYMRU NHS WALES
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University Health Board

R&D
RESEARCH & DEVELOPMENT
Abertawe Bro Morgannwg University Health Board

TITLE OF THE PROTOCOL:

ALOPECIA IN **S**URVIVORS OF **CR**ITICAL **I**LLNESS: A **M**IXED METHODS STUDY

Short title/Acronym: **ASCRIM study**

Sponsor: **ABMU Health Board**

Representative of the Sponsor:
Jemma Hughes
R&D Manager
R&D Department
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REC reference: **16/NS/0133**

STUDY SUMMARY/SYNOPSIS

TITLE	Alopecia in survivors of critical illness: a mixed methods study
SHORT TITLE	ASCRIM study
Protocol Version Number and Date	Version 5.2 18th October 2017
Methodology	Observational and survey
Study Duration	12 months
Study Centre	Morriston Hospital, ABMUHB Princess of Wales, ABMUHB University Hospital Wales, CVUHB Royal Glamorgan Hospital, Cwm Taf UHB Prince Charles Hospital, Cwm Taf UHB Withybush Hospital, Hywel Dda UHB Glangwili General Hospital, Hywel Dda UHB Bronglais Hospital, Hywel Dda UHB Royal Gwent Hospital, ABUHB Nevill Hall Hospital, ABUHB Wrexham Maelor Hospital, BCUHB Glan Clwyd Hospital, BCUHB Ysybty Gwynedd. BCUHB.
Objectives	1) To investigate the incidence and nature of patient-reported alopecia in survivors of critical illness. 2) To investigate the risk factors for alopecia in survivors of critical illness
Number of Subjects/Patients	400 patients
Main Inclusion Criteria	1) ITU survivors with a ITU length of stay of ≥5 days 2) Patients aged 18 years or more with capacity to consent and complete survey
Statistical Methodology and Analysis	Quantitative data analysis: Results from the data collection forms in the ICU and survey responses will be presented descriptively using numbers and percentages (categorical data) or median and interquartile ranges (continuous data). Risk factors will be analysed using Fisher's Exact test and multivariable logistic regression on SPSS (Chicago, Version 22). Missing data will be handled in the final analysis using a multiple imputation system.

Protocol Agreement Page

The clinical study as detailed within this research protocol **(Version XXX, dated XX XXX XX)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

Add as necessary

Protocol Description/Guidelines

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1. INTRODUCTION

1.1 Background / 1.2 Preclinical Data

Alopecia in adult survivors of critical illness has received limited attention in critical care research. During the acute critical illness phase, alopecia is of minimal concern to the intensive care team, when patient survival is the primary objective of care given. In the recovery phase of illness however, alopecia can prove distressing for the patient. Telogen effluvium is a form of non-scarring alopecia associated with the unanticipated termination of the normal growth phase in the hair follicle.(1) Telogen effluvium has been reported to occur after severe psychological stress, multisystem illness and with drug administration.(2-4)

Another type of hair loss that has been reported to occur in the critically ill paediatric population is traction alopecia and is caused by repetitive rubbing of the head on the pillow in patients confined to bed. This type of alopecia results in hair loss to a specific part of the head, normally the occiput.(5) Occipital alopecia and / or pressure sores were reported in 35% of patients in a recent study investigating outcomes in UK military casualties.(6) Limited research exists to date examining the epidemiology of alopecia in survivors of critical illness.

1.3 Clinical Data

In response to the work investigating alopecia in military survivors of critical illness(6), we undertook a small pilot study to investigate the incidence and nature of patient-reported alopecia in civilian survivors of critical illness. A total of 75 patients who had been discharged home for at least 12 weeks from our general ICU, attending the Follow-Up Clinic in 2014, completed a pre-designed alopecia survey. Median age was 65 years, with 35% males and a median ICU length of stay of eight days. A total of 17% of patients reported suffering alopecia. The severity of hair loss ranged between less than 10% to over 50%, with the location of hair loss varying between the patients. Duration of alopecia lasted between three weeks to seven months. The type of hair loss varied between patients, with only one patient reporting the additional loss of non-scalp hair. Five patients reported that complete regrowth had not occurred by the time they attended the clinic. There were no significant differences in demographic variables between the patients with and without alopecia.

The percentage of patients reporting alopecia was lower (17% versus 35%) than that reported by Scott et al (2014).(6) This could be due to the higher injury severity and longer median length of stay reported in the military cohort. The military cohort was also younger and all patients male, so further research into age and sex as risk factors for alopecia may be warranted. On analysis, no significant differences were found between the patients with and without alopecia in terms of age, sex, primary admission diagnosis and APACHE II score.

1.4 Rationale and Risks/Benefits

There are no known risks involved with participation in this non-interventional study. It is an observational study initially, with participants being requested to complete a short survey at the end of the data collection period. The potential benefit of the study is that risk factors for alopecia in critical illness survivors may be identified and care given to future high risk patients may be adapted accordingly.

2. TRIAL OBJECTIVES AND DESIGN

2.1 Trial Objectives

Primary Objective:

To investigate the incidence and nature of alopecia in adult survivors of critical illness

Secondary Objective:

To investigate the risk factors for alopecia in adult survivors of critical illness

Primary Endpoint:

Patient reported alopecia, measured using a pre-designed survey

Secondary Endpoint:

Patient reported alopecia, measured using a pre-designed survey

2.2 Trial Design

Mixed methodology study: Prospective observational and qualitative methods

Setting and sample

The study will be multi-centred, led from Morriston Hospital. There is currently no standardised protocol used for the assessment and measurement of alopecia on our ITU. All patients who survive their admission to ITU, between June and October 2017 and have an ITU length of stay of 5 or more days will be included in this study.

Definition of variables

The risk factors under investigation are the following: APACHE II score, age, primary admission diagnosis, fever, mechanical ventilation days, length of stay, sepsis, all relevant medications (known to cause alopecia), or transfusions during the ITU stay. This information will be collected prospectively during the patient's ITU stay. The Acute Physiology and Chronic Health Evaluation (APACHE II) score is used to predict mortality in ICU patients. The diagnosis of severe sepsis will be given using the definition provided by the 'Surviving Sepsis Campaign' (2008). Patients' primary admission diagnoses will be classified as either surgical (including abdominal, maxilla-facial, spinal, vascular conditions), general medical (including renal, oncology, respiratory conditions), neurological (acute and chronic) and trauma. 'Mechanical ventilation days' will be defined as the number of days the patient required invasive mechanical ventilation. ITU length of stay will be defined as the number of whole days the patient was managed on ITU or the high dependency unit (HDU).

Study design

In order to address both aims of this study a mixed methods approach will be used. An observational design for the prospective data collection and analysis of potential risk factors will be used, with a survey design for the survey completion. The patients recruited in the prospective study will be used for the questionnaire stage of the study, in order that the risk factors for alopecia can be investigated.

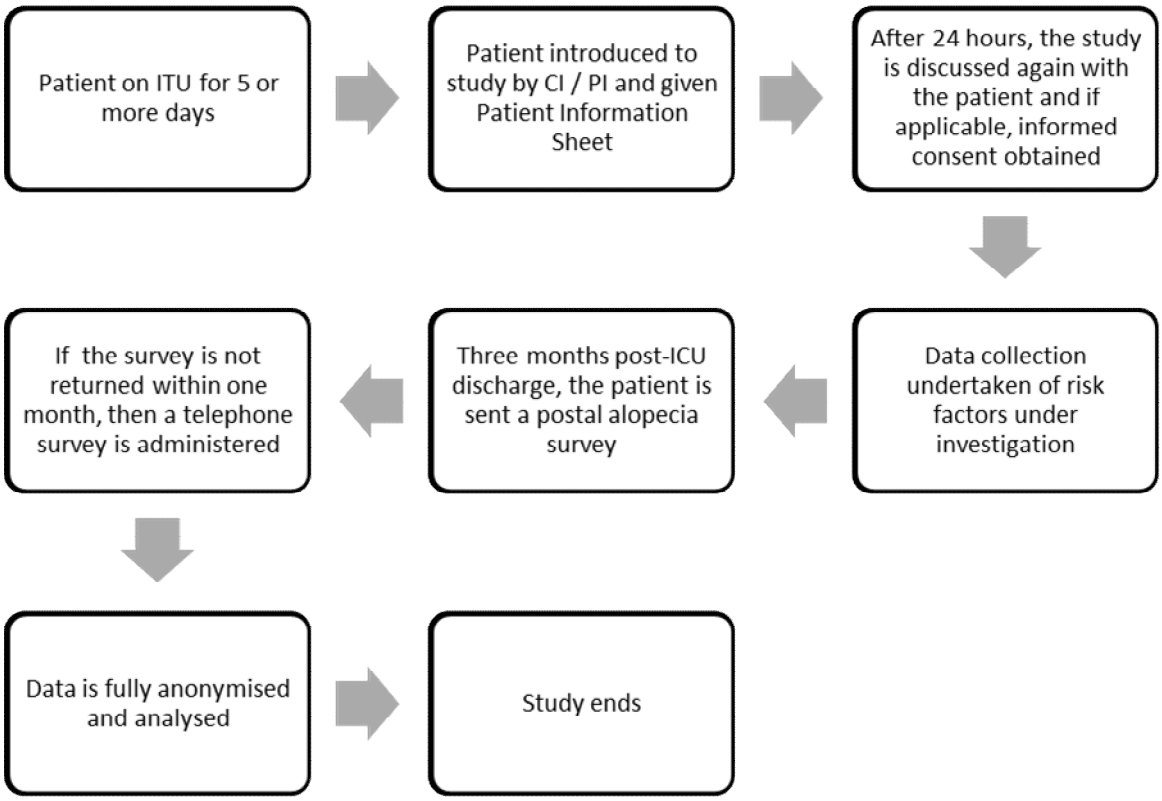
Prospective study: Data will be collected for all patients who survive an ITU length of stay of five or more days. Data will be recorded on a pre-designed spreadsheet and each patient will be allocated a study number.

Questionnaire study: This part of the study will be designed following available guidelines in questionnaire research and the guidelines published in a series of papers in the British Medical Journal.(7,8) A short questionnaire has been designed for the purpose of investigating incidence and nature of alopecia. The survey will be posted to the patients at three months post-ITU discharge, but if no reply is received after one month, then the survey will be administered over the telephone. In order to assess the clinical sensibility of the questionnaire, it was piloted on a number of ITU survivors attending our follow up clinic and as a result, a number of alterations were

made to the survey design. Both closed and open-ended questions are used in the survey.

The survey responses will be entered onto a paper case report form. Any survey with missing demographic data will still be included in the study and the remaining responses included in the analysis. Response rates will be recorded and non-responder analysis will be completed to compare the characteristics of the non-responders and the responders. Patients will be identified only by their hospital numbers once completed surveys are received.

2.3 Study Scheme Diagram



3. Subject Selection

3.1 Number of Subjects and Subject Selection

All patients admitted to ITU with a length of stay of 5 or more days, fitting the study inclusion criteria, will be approached to participate in the study. The number of patients we aim to recruit to the study is 400 over a two month data collection period, in the ITUs of all Welsh hospitals. (Over a two month period in Morriston Hospital alone, there were over 100 patients with an ITU length of stay of 5 or more days). This allows for loss to follow up and non-response to the survey.

3.2 Inclusion Criteria

- Aged 18 years or more
- Capacity to consent to participation
- Capacity to complete survey
- ITU stay of five or more days
- Survived to three months post ITU discharge

3.3 Exclusion Criteria

- Aged less than 18 years
- No capacity to consent to participation
- No capacity to complete survey
- ITU stay of less than five days
- Does not survive to three months post ITU discharge
- Patients requiring chemotherapy that will potentially cause alopecia
- Patients who suffer with any pre-existing alopecia requiring dermatology input
- Patients who suffer with complete baldness

3.4 Criteria for Premature Withdrawal

- Death
- Patient request for study withdrawal

4. Study Procedures

4.1 Informed Consent Procedures

Consent will be obtained for participation in the study when the patient is awake / conscious and able to provide informed consent. Informed consent will be obtained by the chief or principal investigators who will all receive 'protocol and informed consent specific training' in alignment with the principles of GCP. Consent will be obtained following a full introduction to the study and once the patient has had time to discuss the Patient Information Sheet with a family member / carer (as appropriate). The participants will be given 24 hours to consider participation. A study withdrawal letter will also be attached to the Patient Information Sheet in case the patient wishes to withdraw consent at a later date.

4.2 Screening Procedures

All patients admitted to ITU with a length of stay of 5 or more days, fitting the study inclusion criteria, will be screened for potential participation in the study, by the chief or principal investigators. A screening log will be maintained throughout the study period.

4.6 Follow up Procedures (if applicable)

At three months post-ITU discharge, the patient will be sent a survey in the post. If there is no reply to the postal survey after one month, the CI / PI will contact that patient and administer the survey by telephone.

4.9 End of Study Definition

The study will end when all data has been collected and all surveys are completed. A six month period following end of patient recruitment will be used for completion of the second CRF and data cleaning / validation

4.11 Subject Withdrawal

A patient can withdraw from the study at any time during the data collection period. They will have a study withdrawal letter that can be sent to the CI at any time.

4.11 Data Collection and Follow up for Withdrawn Subjects

Any patient who withdraws consent will have their data removed from the study.

6. Safety Reporting

As this is a non-interventional study, there are no safety reporting issues to consider

7. Statistical Considerations

7.1 Primary Endpoint Efficacy Analysis

Patient reported alopecia as measured by a pre-designed survey

7.2 Secondary Endpoint Efficacy Analysis

Patient reported alopecia as measured by a pre-designed survey

7.3 Safety Endpoints

N/A

7.4 Sample Size

We aim to include sufficient patients in order that we can present the unadjusted and adjusted odds ratios and 95% confidence intervals for the risk factors for alopecia in survivors of critical illness. Vittinghoff and McCulloch (2007) suggested that the number of patients needed to ensure sufficient power in a cohort study is equivalent to five to nine events per variable (EPV) being investigated.(9) We will therefore use an EPV of 7 for this study. In this study we aim to investigate ten variables or risk factors therefore a minimum of 70 events (incidence of alopecia) were required. The previous pilot study completed by our research team reported an incidence of alopecia of 17% in survivors of critical illness, so we calculate that we need at least 400 patients in total. It would take two months to provide a sample of 400 patients (with a length of stay of 5 days to more) in the ITUs of all Welsh Hospitals, so we aim to recruit patients for four months to allow for mortality and loss to follow up.

7.5 Statistical Analysis

Results will be presented descriptively using numbers and percentages (categorical data) or median and interquartile ranges (continuous data). Risk factors will be analysed using Fisher's Exact test and multivariable logistic regression on SPSS (Chicago, Version 22). Missing data will be handled in the final analysis using a multiple imputation system.

8. Data Handling & Record Keeping

8.1 Confidentiality

The CI will take responsibility to ensure that patient anonymity is protected and maintained. The CI will also ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

All patients will be allocated a study number once informed consent is obtained. Personal data will only be identifiable by this study number during data collection. Data collection will only include the risk factors (as outlined earlier). All patient identifiable data will be removed and data completely anonymised once data collection using the survey is completed. Data will be stored on a Health Board, password encrypted computer, only accessible to the CI / PIs of the study team. The

CI will act as the custodian of the data. The Caldicott Guidelines will be adhered to throughout the study.

8.2 Study Documents

A copy of the patient consent form, Patient Information Sheet, study withdrawal letter and case report form is attached to this submission. A Trial Management file will be used and all hard copies (as listed below), will be kept in a locked room within the physiotherapy department.

- A signed protocol and any subsequent amendments
- Sponsor Self-Monitoring template for the trial team to complete on a regular basis as detailed by the Monitoring section
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Signed site agreement
- Ethics submissions/approvals/correspondence
- CVs of CI and site staff
- Delegation log
- Staff training log
- Site signature log
- Patient identification log
- Screening log
- Enrolment log
- Monitoring visit log
- Protocol training log
- Correspondence relating to the trial
- Communication Plan between the CI/PI and members of the study team

8.3 Case Report Form

A copy of the case report form is attached to this submission

8.4 Record Retention and Archiving

During the course of research, all records will be the responsibility of the Chief Investigator and will be kept in secure conditions. Once the research trial is complete, the records will be kept securely for a further 5 years in the Health Board archive facility.

8.5 Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

8.6 Clinical Governance Issues

8.6.1 Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee must be obtained and subsequently submitted to the Research & Development Department to obtain Final R&D approval.

8.7 Quality Control and Quality Assurance

8.7.1 Summary Monitoring Plan

The Research Governance Manager will monitor this study in accordance with Health Board Policy

8.7.2 Audit and Inspection

Auditing: Definition “A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).”

This study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.
2. An individual investigator or department may request an audit.
3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
5. Projects may be randomly selected for audit by an external organisation.

Internal audits will be conducted by a sponsor’s representative

8.8 Non-Compliance

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

9. Trial Committees

There will be no Trial Steering Committee or Data Management Committee set up for this study

10. Publication Policy

The pilot work to this study was published as a letter in the Journal of the Intensive Care Society. The aim would be to publish the results of this study in Critical Care Medicine (high impact, peer-reviewed international journal) and a recent email from the Editor suggested that they would be very interested in receiving our submission.

11. References

1) Fatani MI, Bin mahfoz AM, Mahdi AH et al. Prevalence and factors associated with telogen effluvium in adult females at Makkah region, Saudi Arabia: A retrospective study. *Journal of Dermatology & Dermatologic Surgery* 2015; 19:27–30.
2) Tosi A, Misciali C, Piraccini BM, et al: Drug induced hair loss and hair growth. Incidence, management, and avoidance. *Drug Saf* 1994; 10:310–317.
3) Sperling LC. Hair and systemic disease. *Dermatol Clin* 2001; 19:711–726.
4) Bernstein, GM, Crollick, JS, Hassett, JM. Post-febrile telogen effluvium in critically ill patients. *Crit Care Med* 1988; 16:98–99.
5) Pettignano R, Heard ML, Labuz MD et al. Hair loss after extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2003; 4:363-366.
6) Scott T, Davies M, Cummings I et al. Intensive care follow-up in UK military casualties: a one year pilot. *Journal of the Intensive Care Society* 2014;15:113-116.
7) Boyton PM. Administering, analysing and reporting your questionnaire. *BMJ*. 2004; 328:1371-1375.

8) Boyton PM, Greenhalgh T. Selecting, designing and developing your questionnaire. *BMJ.* 2004;328:1312-1315.

9) Vittinghoff E, McCulloch C. Relaxing the rule of ten events per variable in logistic and cox regression. *Am. J. Epidemiol*. 2007 165:710-718.

12. Appendices

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor