Writing a Research Protocol

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Aims of this presentation

- Importance of the protocol
- Point you towards protocol templates
- Standard sections
- Identify key sections
- Help you draft protocols suitable for approval and use by the trial team

Question

Have you read a protocol?

Have you written a protocol?

Why is a protocol important?

- Medicine for Human Use (Clinical Trials) Regulations 2004:
  - A document that describes the objective(s), design, methodology, statistical considerations, and organization of a clinical research project.
- Required for approvals: Sponsor, REC, NHS R&D and MHRA
- Standardises trial population and data across sites
- Allows others to recreate the trial
- Should be published as a statement of intent

Protocol is an Essential Document

Provides foundation for:

- Participant Information Sheet/Informed Consent
- Operations manuals and sample handling
- Statistical analysis
- Data Management Plan

Usually template driven

- CTIMPs: HRA template: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/
- Non-CTIMPS: adapt CTIMP template
- Qualitative Research template : above web link

Version control (See TASC SOP)

- Drafts version 0.1, 0.2
- DRAFT Version 1 submitted for sponsor approval
- Version 1 submitted for regulatory approval

Question

Who should read the trial protocol?

Audience

- Funders
- Sponsors
- Regulatory authorities
  - Research Ethics Committee (REC)
  - NHS R&D
  - Medicines and Healthcare products Regulatory Agency (MHRA)

- Sites
  - Principal Investigators
  - Research Nurses
- Trial Management Team
- Data Management Team
- Statisticians
- Academic collaborators

- Get input from stake holders at an early stage

Patient and Public Involvement and Engagement (PPIE)

- Pre-award input
- Relevance to the patient population and their family/carers
- Acceptability and burden
- Host organisation may have access to PPIE groups

HRA CTIMP Protocol Development Tool: Contents

HRA CTIMP Protocol Development Tool

NHS
Health Research Authority

SHORT TITLE/ACRONYM

EudraCT number

FULL/LONG TITLE OF THE TRIAL

Aim: To identify the Trial to enable retrieval from literature or internet searches. It should be immediately evident what the trial is investigating and on whom to allow rapid judgment of relevance.

For intervention or exposure studies a structured title should contain:

- Information on participants
- Intervention (exposure)
- Comparison groups
- Outcomes
- Phase
- Trial design

SHORT TRIAL TITLE / ACRONYM

Aim: To provide a summary of the long title. It is usually the title used on information sheets and consent forms for research participants or others giving consent or assent on their behalf.

The short title should be:

- Sufficiently detailed to make clear to participants what the research is about in simple English
- If acronyms are used the full title should explain them. The proposed acronym should not drive the long title

II. Trial Summary

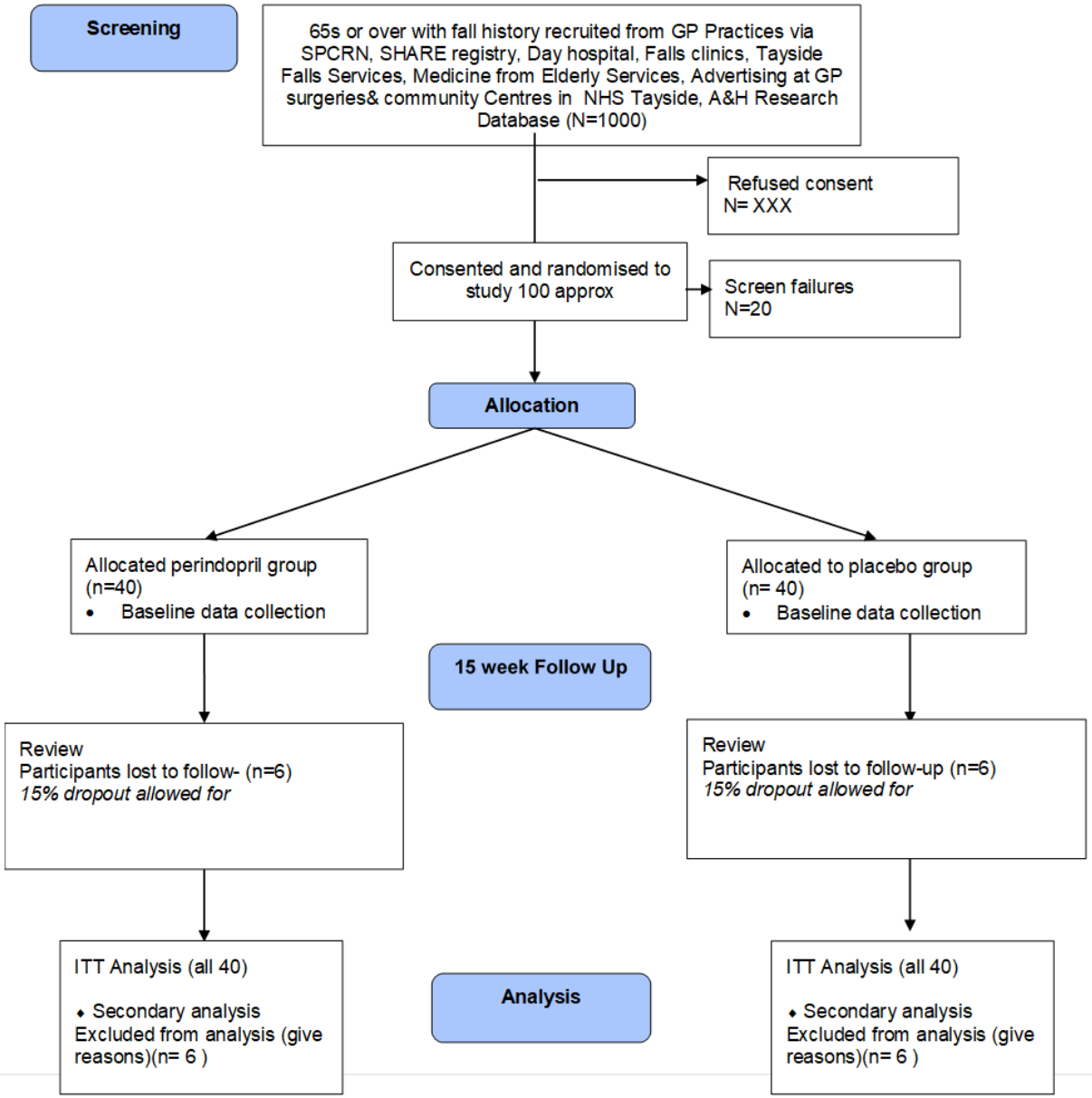
Design:	Multi-centre, randomized, double-blind, placebo controlled, parallel group trial with four treatment arms
Clinical Phase:	IV
Participants:	Adults at high risk of falls
Sample size:	96 participants, randomised to placebo or intervention arms
Duration:	Total duration 36 months, recruitment 24 months, treatment for 12 months
Objectives:	To test which dose of oral Vitamin K (200mcg or 400mcg) most improves anteroposterior sway compared to placebo
	To evaluate the safety and tolerability of Vitamin K
Outcomes Measures:	Between-group difference in anteroposterior sway at 12 months, measured using the AMTI sway platform
	Recording AEs, SAEs and withdrawals
IMP/Intervention:	Vitamin K 200 or 400 micrograms versus placebo, oral tablet, once daily for 1 year

VIII: Trial Flow Chart

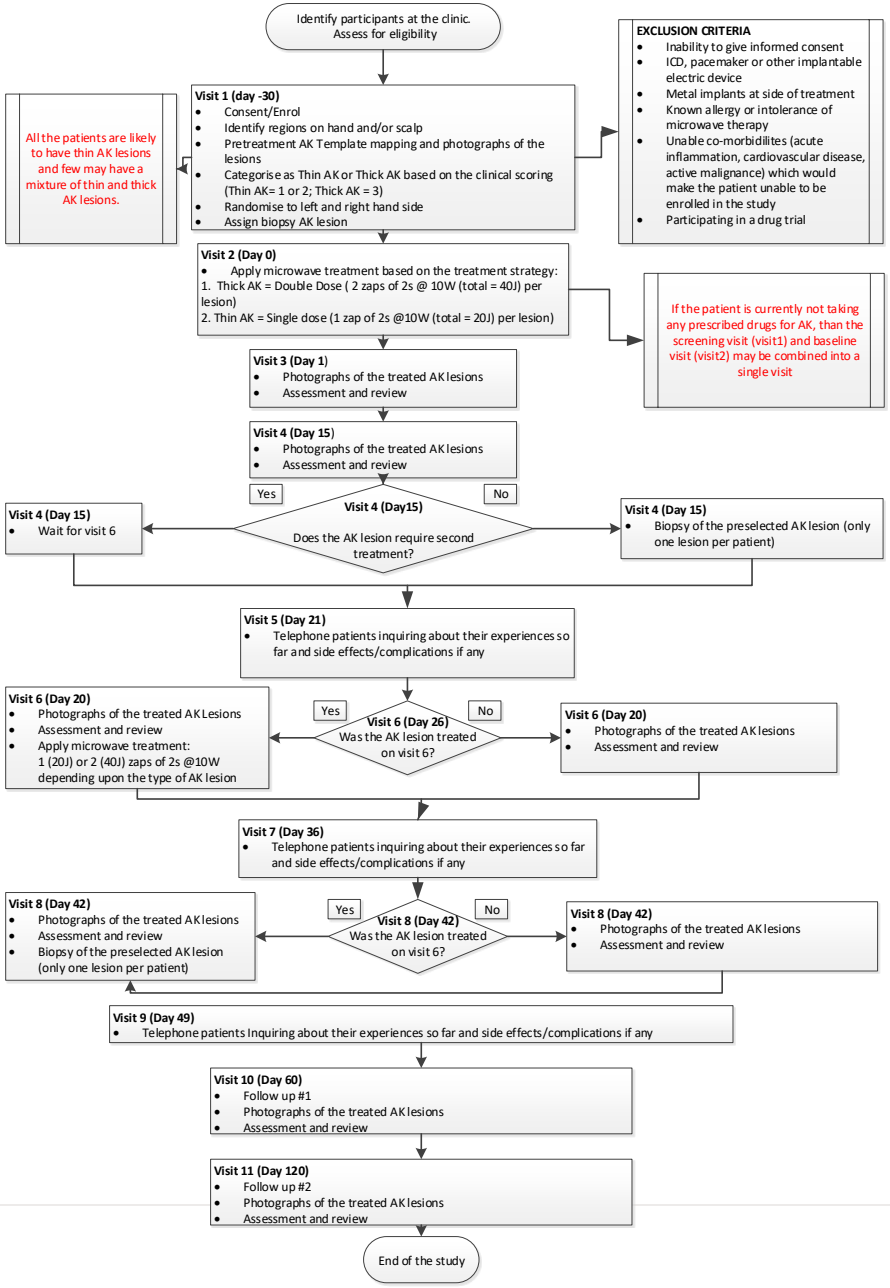
- *"…to ensure that the protocol is sensibly structured and ordered to allow users of the document to follow the patient and trial pathway accurately and with ease."*
- Shows the design of the trial, recruitment, screening, timings of visits, and details of assessments and procedures
- Simplified version could be used in Participant Information Sheet

CONSORT flow chart

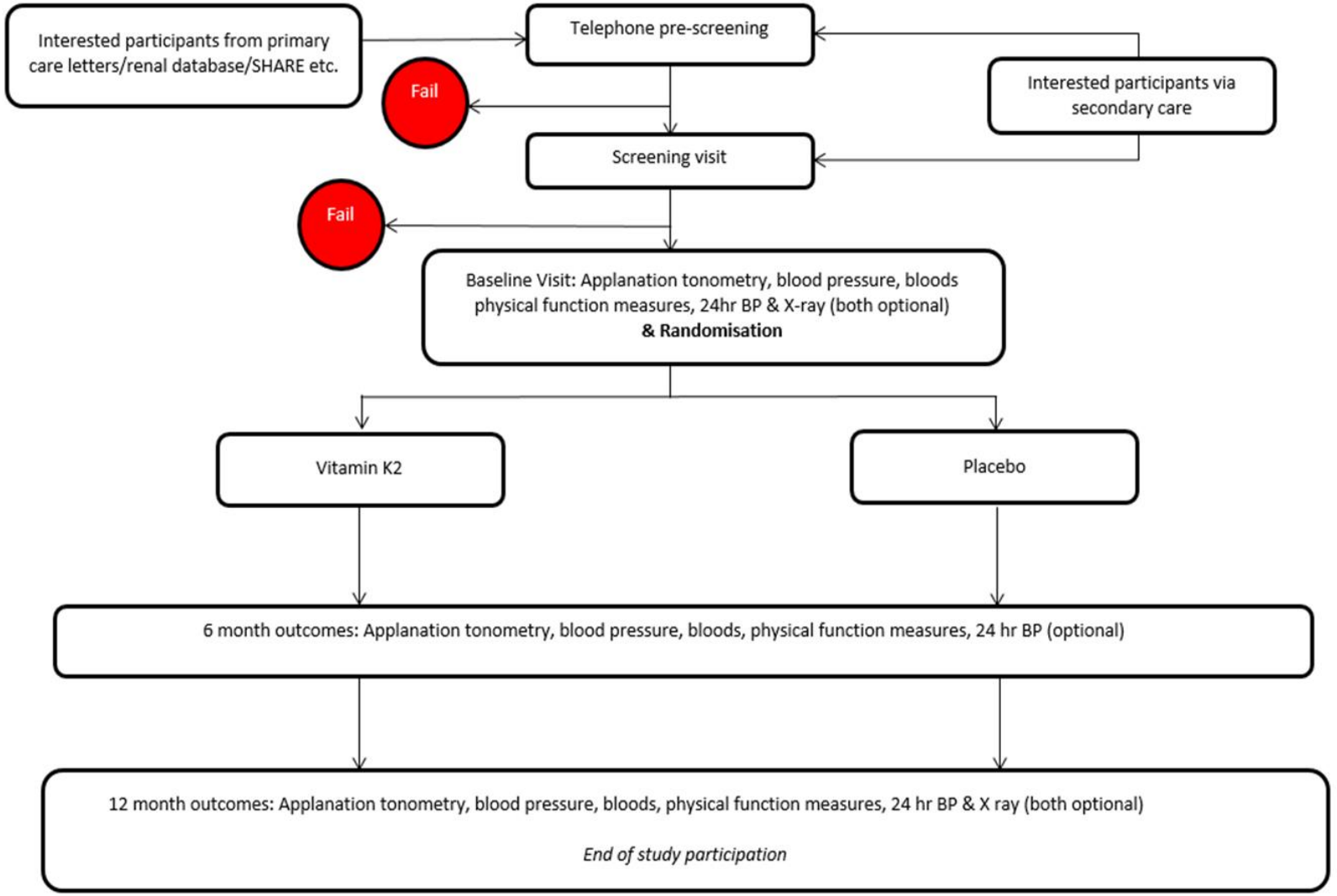
Guidelines on how to publish findings from clinical trials



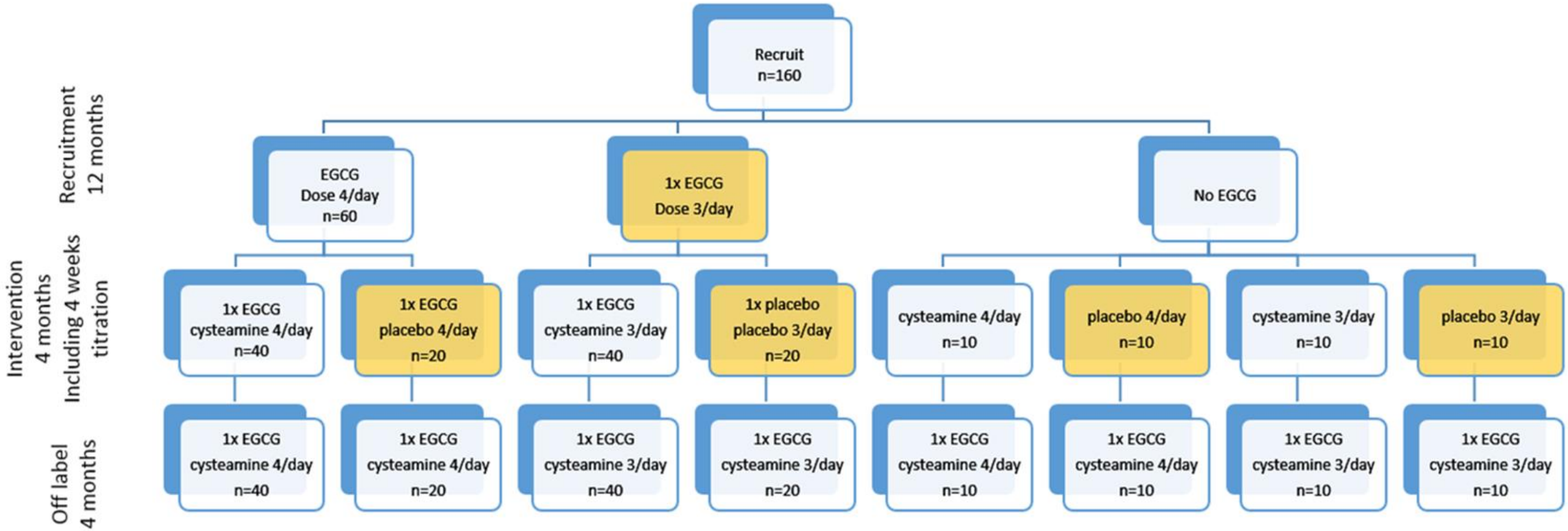
Single Arm


Identify participants at the clinic. Assess for eligibility
EXCLUSION CRITERIA
Inability to give informed consent
ICD, pacemaker or other implantable electric device
Metal implants at side of treatment
Known allergy or intolerance of microwave therapy
Unable co-morbidilites (acute inflammation, cardiovascular disease, active malignance) which would make the patient unable to be enrolled in the study
Participating in a drug trial
All the patients are likely to have thin AK lesions and few may have a mixture of thin and thick AK lesions.
Visit 1 (day -30)
Consent/Enrol
Identify regions on hand and/or scalp
Pretreatment AK Template mapping and photographs of the lesions
Categorise as Thin AK or Thick AK based on the clinical scoring (Thin AK= 1 or 2; Thick AK = 3)
Randomise to left and right hand side
Assign biopsy AK lesion
Visit 2 (Day 0)
Apply microwave treatment based on the treatment strategy:
1. Thick AK = Double Dose (2 zaps of 2s @ 10W (total = 40J) per lesion)
2. Thin AK = Single dose (1 zap of 2s @10W (total = 20J) per lesion)
If the patient is currently not taking any prescribed drugs for AK, than the screening visit (visit1) and baseline visit (visit2) may be combined into a single visit
Visit 3 (Day 1)
Photographs of the treated AK lesions
Assessment and review
Visit 4 (Day 15)
Photographs of the treated AK lesions
Assessment and review
Visit 4 (Day15)
Does the AK lesion require second treatment?
Yes
No
Visit 4 (Day 15)
Wait for visit 6
Visit 4 (Day 15)
Biopsy of the preselected AK lesion (only one lesion per patient)
Visit 5 (Day 21)
Telephone patients inquiring about their experiences so far and side effects/complications if any
Visit 6 (Day 20)
Photographs of the treated AK Lesions
Assessment and review
Apply microwave treatment:
1 (20J) or 2 (40J) zaps of 2s @10W depending upon the type of AK lesion
Visit 6 (Day 26)
Was the AK lesion treated on visit 6?
Yes
No
Visit 6 (Day 20)
Photographs of the treated AK lesions
Assessment and review
Visit 7 (Day 36)
Telephone patients inquiring about their experiences so far and side effects/complications if any
Visit 8 (Day 42)
Photographs of the treated AK lesions
Assessment and review
Biopsy of the preselected AK lesion (only one lesion per patient)
Visit 8 (Day 42)
Was the AK lesion treated on visit 6?
Yes
No
Visit 8 (Day 42)
Photographs of the treated AK lesions
Assessment and review
Visit 9 (Day 49)
Telephone patients Inquiring about their experiences so far and side effects/complications if any
Visit 10 (Day 60)
Follow up #1
Photographs of the treated AK lesions
Assessment and review
Visit 11 (Day 120)
Follow up #2
Photographs of the treated AK lesions
Assessment and review
End of the study

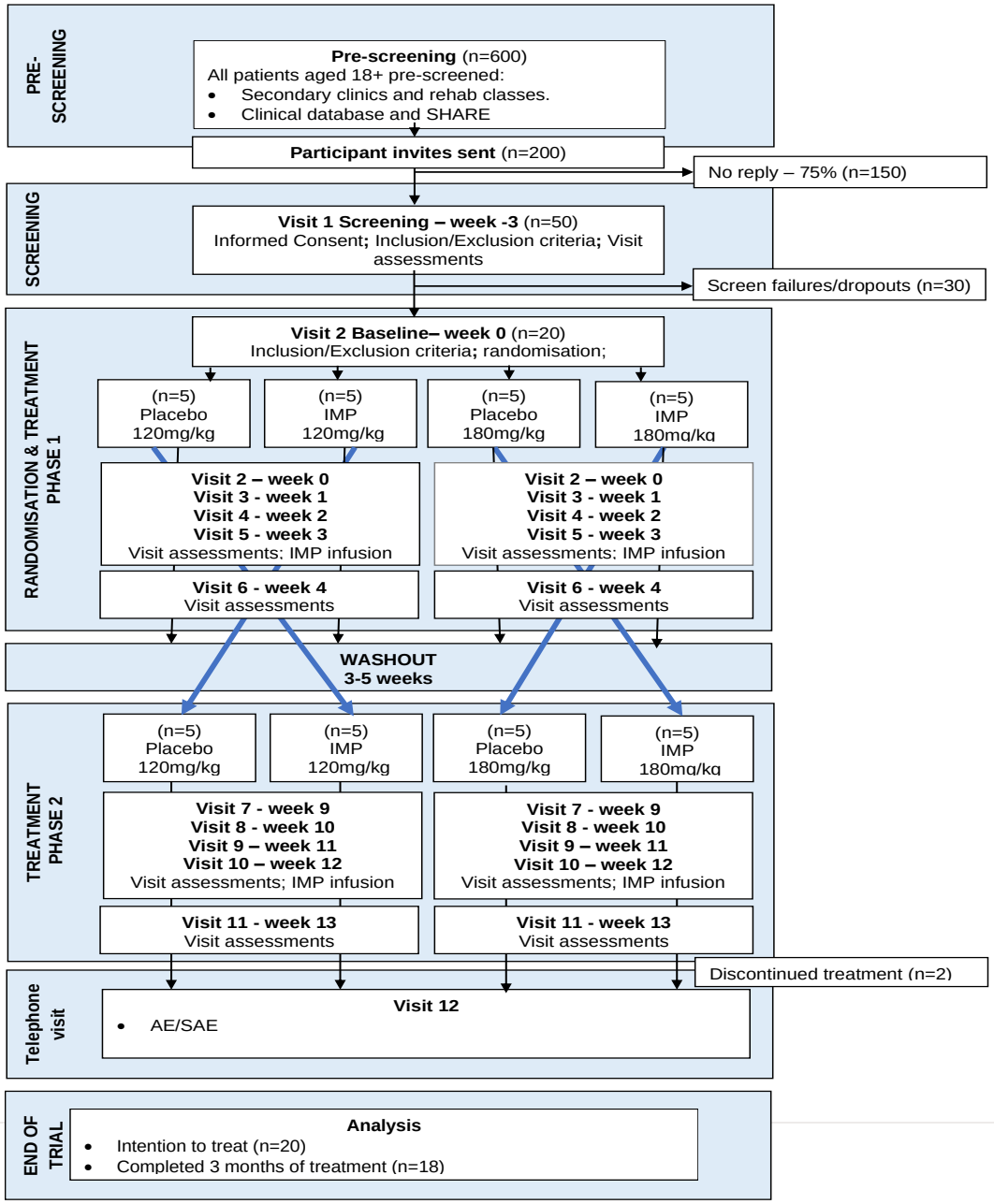
Parallel Arm



Complex Parallel Arm



Cross over design



3. Objectives and Outcome Measures/Endpoints

What change are you trying to detect (**OBJECTIVE**), how will you assess this change (**OUTCOME MEASURE/ENDPOINT**), when will assess this change (**TIMING**)

Outcomes must be:

- Validated, reproducible, relevant to the intervention and clinical condition
- Core Outcome Sets (COS) e.g. COMET https://www.comet-initiative.org/

Can be:

  - clinical assessments e.g. BP, 6 MWT, biomarker, number of falls, SAEs
  - Validated questionnaire e.g. QoL, Asthma Assessment Tool
  - Participant preference e.g. structured interview
- Trial may be to identify most appropriate OM for future study, or a pilot to determine recruitment rates, acceptability etc.
- Involve participants in selecting OM
- Consider patient burden
- Include health care providers
- DO NOT HAVE TOO MANY

Table of Outcomes and Endpoints

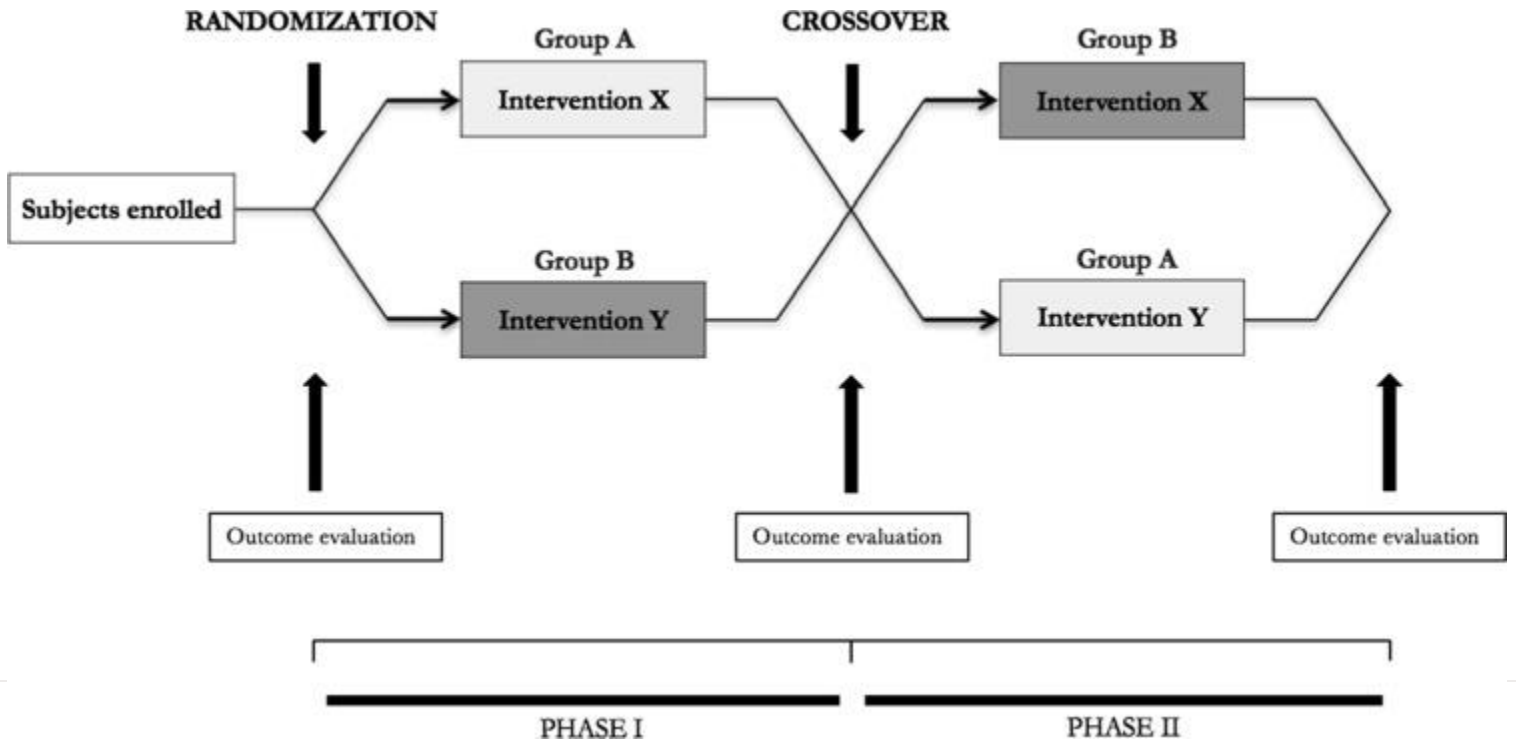
Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To determine the sensitivity of fluorescence imaging alone for SLN identification compared with a combination of ICG and a standard tracer (blue dye or radioisotope)	Percentage of patients with successful identification of the SLN using ICG alone or combined with a standard tracer, stratified by cohort	At the time of SLN biopsy
Secondary Objectives Procedural node positivity rates	Proportion of SLN biopsy cases with tumour deposits in at least one node (including macrometastases, micrometastases and isolated tumour cells)	Post-surgery, when histopathology results are available
Adverse events from SLN biopsy	Seroma formation Cutaneous staining Other adverse reactions to tracers	2 weeks and 3 months

4. Trial Design

"To describe the ideal design for the research question and what the trial is designed to show."

Examples:

- Multi-centre, randomized, double-blind, placebo controlled, parallel group trial with four treatment arms
- Observational study with specimen collection.
- Double-blind, randomized, cross-over trial



6. Participant Eligibility Criteria

Defines the trial population

- Applied consistently throughout the trial
- Consider timelines and flexibility to avoid arbitrary or unworkable definitions
- Inclusion criteria: define the population the trial is aiming to include
- Exclusion criteria: excludes sub-groups, e.g. for safety reasons or burden
- Age
- Sex
- Clinical parameters clearly defined, e.g. type 1 diabetes alone or with cardiovascular disease

7. Trial Procedures

Participant Pathway:

- Timing of visits and where they will take place
- Participant Identification and Recruitment
- Screening and enrolment process
- Consent
- Randomisation
- Trial assessments
- Management of biological samples

Participant Recruitment and Consent

Identify all routes used to identify participants at the start

- Clinic
- GP
- Databases, e.g. departmental, SHARE
- Advertisements

Who will be taking consent

- Consider patient population
- How with information be provided to ensure Informed Consent
- Consent must be in place before any trial specific assessments are carried out
- Clinician available

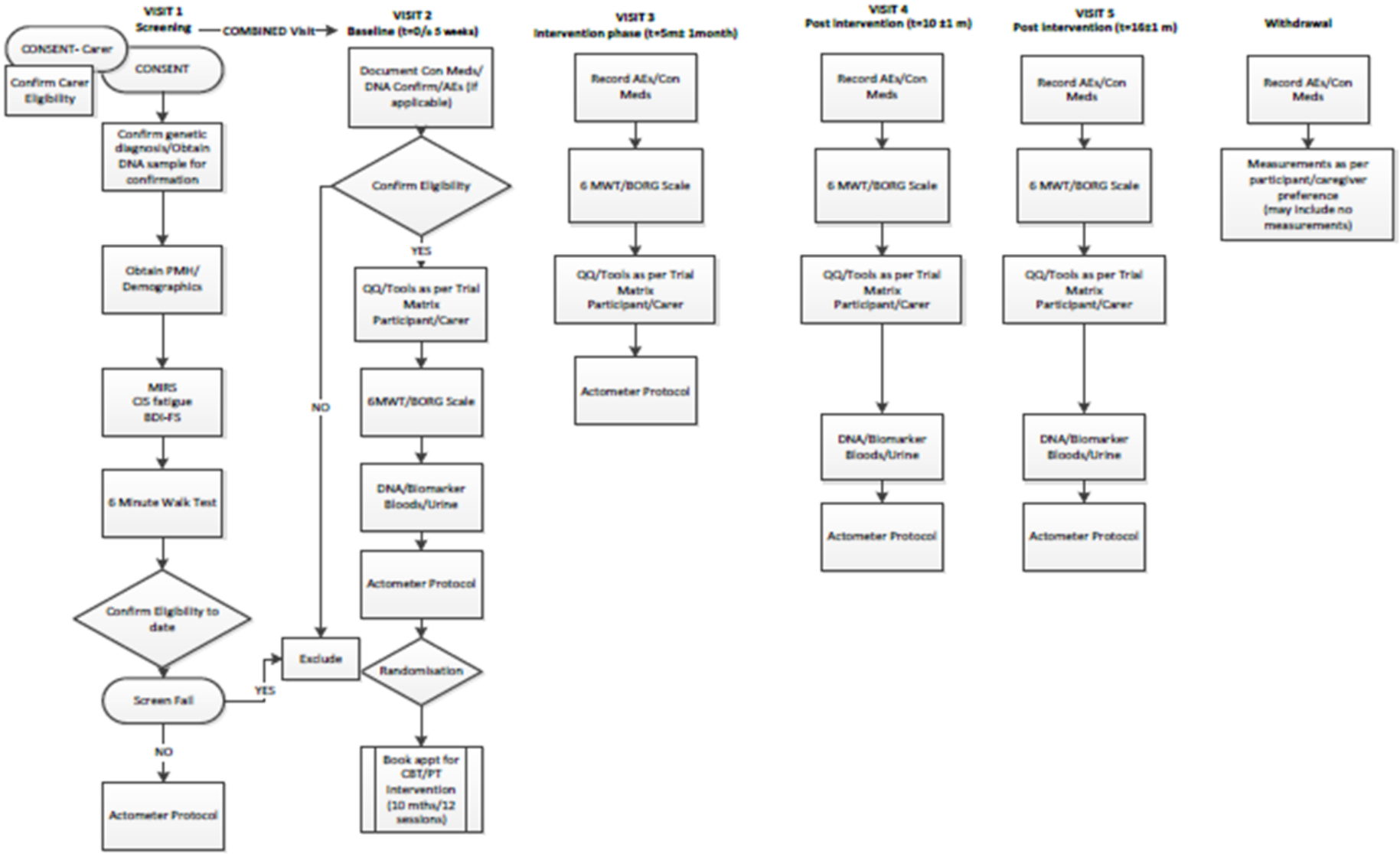
Schedule of Procedures (Trial Matrix) as an Appendix

- Trial Matrix
  - What happens to a participant at each visit
  - Everything being done to a participant while on the trial, including routine care, outcomes and safety
  - Needed for budget preparation
- Simplified version could be used in Participant Information Sheet

Trial Matrix

	Visit 1[1]	Visit 2[1]	Visit 3	Visit 4	Visit 5	Visit 7	Visit 7	Visit 8
Type of Visit	H Screening	H Baseline	H	☎	H	H	☎	H
Timeline	-35 days	Day 0 (+/-3 days)	Day 15 (+/-3 days)	Day 21 (+/-3 days)	Day 28 (+/-3 days)	Day 42 (+/-3 days)	Day 49 (+/-7 days)	Day 120 (+/-7 days)
Informed consent	X							
Inclusion/exclusion	X							
Medical History	X							
Record other medication	X	X	X	X	X	X	X	X
Physical Examination	X	X	X		X	X		X
Map AK	X	X	X		X	X		X
Photograph AKs	X	X	X		X	X		X
Randomisation	X							
Pre select AK for biopsy	X							
Microwave treatment		X			X[2]			
Visual assessment of AKs		X	X		X	X		X
Biopsy			X[3]			X[3]		
Patient acceptability		X	X	X	X	X	X	X
Record Adverse Events		X	X	X	X	X	X	X

Participant Pathway



8. Trial Treatment

Trial treatments or interventions and controls, details of:

- investigational drug
- placebo
- device
- surgery
- behavioural change
- exercise regime
- text messages
- standard care

9. Pharmacovigilance

Adverse Events, Serious Adverse Events

- Template will define AE, SAE, SAR, SUSAR etc.
- Captured from consent
- Assessed at every visit
- All AEs recorded in AE log
- Different reporting for CTIMPs and non-CTIMPS
- Expected SAEs for a population or intervention may not need immediate reporting to sponsor
- Example:

"Worsening of bronchiectasis during the trial will not be classed as an AE, but is defined as an outcome. Hospitalisations resulting from worsening of bronchiectasis are common events for patients with bronchiectasis and therefore will be recorded but not reported to sponsor. The exception to this is when, in the opinion of the investigator, there is causal relationship between the trial drug and the hospitalisation for bronchiectasis."

10. Statistical Analysis

- Sample size calculation
  - Clinically significant difference e.g. gold standard, current therapy or intervention versus no intervention
  - Pilot and feasibility studies don’t always need a sample size
- Primary outcome analysis
- Secondary outcome analysis
- Statistical Analysis Plan (SAP): separate to protocol section, must be completed before data lock
- Published protocol states intent

11. Data Management

- What data will be collected
  - Source data e.g. hospital records, lab notes, participant dairies etc.
  - Standardised tool, e.g. McGill pain score, vs non-standard
- Data Management System: bespoke, Excel, other
- How data quality will be managed, maintain audit trail, access to the system, minimise missing data, back up and archiving
- Sharing data after the trial
- Data Management Plan

- Case Report Form design

Protocol Amendments

- Not unexpected so should be costed
- Required if needed to improve the delivery of the trial
- Consider impact on timelines, budgets, resources, statistical analysis, supporting documents and other sections of the protocol
- Involve stakeholders in the decision to make an amendment
- Amendments have to go through the approval process before implementing

In summary

- Have a clear research question
- One primary objective and limited secondary objectives
- Well defined and limited outcome measures
- Defined participant population but consider pragmatic versus explanatory
- Other protocol sections such as Data Management, Monitoring etc.
- Be considerate of the participant population
- Involve participants in the design
- Publish your protocol
- Do what you said you would do
- Look at other published protocols
- Advice is available from TCTU

Thank You

Questions

Contact: TCTU@dundee.ac.uk