PROTOCOL FOR PHASE 1 CLINICAL TRIAL TO DETERMINE MAXIMUM TOLERABLE DOSE OF AFRICAN BITTER ROOT FOOD SUPPLEMENT

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APPROVALS	
_____/EU/_____ Principal Investigator	6th July 2026 Date
_____/KB/_____ Quality Officer of Sponsor	6th July 2026 Date

Revision History		
Revision	Date	Description
A0	9th May 2026	New escalation protocol for trial in ICH M11 CeSHarP format. This document includes changes from pre-submission review comments. ISRCTN Number added ISRCTN51184184 to protocol header.
A1	15th May 2026	Clarification to conflicts of interest includes supply of the intervention, clarification of data protection and Jira GMP Annex 11 status. Opening enrolment to non-English speakers. Dose clarified.
A2	6th July 2026	Removing ambiguities or inconsistencies detected during Stages 1 and 2 of the trial. Detailed list on Page 4. No material change to any part of protocol, no change affecting any actual participant.

CESHARP (M11) SUMMARY

Full Title:	Protocol for Phase 1 clinical trial to determine maximum tolerable dose of African Bitter Root Food Supplement
Trial Acronym:	ABRS-P1-DOSE
Sponsor Protocol Identifier:	ABRS-P1-DOSE
Original Protocol:	A0
Version Number:	A2
Version Date:	6th July 2026
Amendment Identifier:	A2
Amendment Scope:	Global
Sponsor's Investigational Product Code(s):	ABRS-AR-200mg-Cap
Investigational Product Name(s):	African Bitter Root Supplement (ABRS), a herbal food supplement in UK, Europe and Australia
Trial Design:	Double blind 3+3 Dose Escalation.
Trial Phase:	Phase 1
Short Title:	Phase 1 Clinical Trial of African Bitter Root
Sponsor Name and Address:	Deep Life Medical Lda Edificio Forno De Cal, 2 02D, Estrada Nacionale N.378, Sesimbra, 2970-643 Portugal Co-Sponsor Name and Address: Deep Life Medical Ltd 6 Newhailes Industrial Estate, Musselburgh, EH21 6SY, United Kingdom Contact: compliance@deeplifemedical.com The product assessed is a food supplement. The classification of this trial has been confirmed by the HRA tool with certificates issued stating that combined review is not required.
Regulatory or Clinical Trial Identifier(s)	ISRCTN51184184
Sponsor Approval:	9th May 2026 Rev A0, 15th May Rev A1, 6th July 2026 Rev A2

Sponsor Signatory: Alex Deas, PhD 6th July 2026

Head of Research Compliance, compliance@deeplifemedical.com

Medical Expert Contact: Principal Investigator, Dr Emem Usoro, GMC 7266847

Conflicts of Interest:

The Principal Investigator (PI) has no financial conflicts of interest.
The Principal Investigator (PI) is fully independent of the sponsor.

The PI is a registered gynaecologist with formal clinical investigator training. The PI directly observed use of ABRS in a 2023 obstetric case. The PI is not related to any other person in this trial.

DSMB is fully independent of the sponsor and the PI, and comprises a medical doctor. DSMB may be assisted by a cultural or language interpreter employed by the sponsor.

The sponsor's main contact has Advanced Good Clinical Practice training up to date, i.e. current validity.

The sponsor's involvement in this trial is limited to providing the trial schema design, paying receipted expenses, supply of the pre-randomised intervention, use of its QA system including its SPARK Ada trial program "CT Manager" and eDMR for document storage, panel for review of documents and audit to ensure adherence to protocol.

The Sponsor's main contact, discovered ABRS and family members use ABRS. The sponsor's main contact's wife was the ABRS user in the 2023 obstetric case cited. The sponsor therefore, has conflicts of interest, both commercially and by relationship.

No public grants have been received by any party.

Amendment:

This protocol was amended previously. Details of amendments will be presented in Section 11.3 Prior Protocol Amendment(s).

Current Amendment

The table below describes the current amendment.

Approximate Enrolled at Time of Sponsor Approval:	100% of the pool of participants required for the full 4-stage trial has been recruited and screened; dosing is at Stage 2 of 4 (50% complete).	
Reason(s) for Amendment:	Removed ambiguity.	Secondary: Clarifications.
Amendment Summary:	Clarification only. No material change in protocol affecting any participant. See table below/overleaf.	
Is this amendment likely to have a substantial impact on the safety or rights of the participants?	No. This amendment removes ambiguity only, and accommodates feedback from participants that is in their favour. All participants were informed, and the changes have the informed consent of all participants.	
Is this amendment likely to have a substantial impact on the reliability and robustness of the data generated in the clinical Trial?	No. There is no material change to the trial, only improvements to the documentation of the trial to remove potential sources of error arising from ambiguities. The most significant change is the TLE definition. No Grade 1 AE has occurred in Stage 1 or Stage 2 that would be treated differently under the new causality-filtered definition.	

Overview of Changes in the Current Amendment

Description of Change

1. Clarifications to remove possible ambiguities or inconsistencies identified during initial stage of trial, and incorporate participant feedback on changes that help them participate but which have no material effect on either quality of the trial or power factor of results.
2. There is no substantive or actual change affecting any of the actual participants or persons who have enrolled to date.
3. No TLEs or Grade 1 AE has occurred in Stage 1 or Stage 2 that would be treated differently under the new causality-filtered definition.

Brief Rationale for Change

1. Removes an ambiguity in trial scheme flagged by CT Manager, a SPARK Ada program used to create triple blinding of the trial.
2. Resolves other ambiguities or inconsistencies identified during manufacturing of the doses, and executing Stage 1 and first dose of Stage 2.
3. Acceptance of laboratory test results taken up to 90 days prior to participation to avoid unnecessary repeat testing.
4. PIL updated with section added to clarify use of medical examination data and actions in event of discovery of undeclared pre-existing conditions, to document answers to frequently asked questions from participants.
5. Provision of additional support by sponsor for the participants if the medical examinations detect previously unknown pre-existing conditions.

Section # and change

This amendment consists of clarifications identified during the conduct of Stage 1 and the first half of Stage 2 of the Trial, together with two corrective actions arising from a protocol deviation. No change affects any data already collected in Stage 1 or the first half of Stage 2. No Grade 1 AE occurring in that period would have been treated differently under the revised TLE definition below.

1. Governance and blinding

- Cover page: added the Sponsor's audit role to the description of Sponsor involvement.
- Section 1.1.2.3 (Blinded Roles): added disclosure that the Sponsor's representative is blinded in practice (all TLE processing is performed by CT Manager, which does not expose blinding data until trial completion), while noting a residual theoretical risk via destroyed manufacturing files, and stating why this role is not formally listed as guaranteed-blinded.
- Section 11.4 (Committees): DSMB now stated as a single independent GMC-registered doctor. The Sponsor's in-house statisticians are confirmed as available to assist but not formal DSMB members. Cover page conflicts-of-interest wording aligned to match.

2. Trial schema and safety endpoint

- Section 1.2: schema restated as a numbered finite state machine, alongside the earlier narrative sub-clause structure, which has numeric numbering to remove ambiguity in machine-readable processing used in verification of CT Manager implementation. New Section 1.2.1.1 added, setting out special rules and edge cases (e.g. withdrawal between Tub A and Tub B).
- Section 1.2.5: TLE definition clarified to require plausible (possible) causality, or classification as an Unexpected AE; continuation of a pre-existing symptom of a known pre-existing condition is excluded from AE/TLE status (see also Section 9.2).
- Section 10.4.1.3: clarified that a withdrawal with no TLE reported requires participant replacement and the stage to be rerun, with no TLE recorded, reconciled with Section 1.2.1.1 to remove a prior internal inconsistency.
- Section 1.1.2.2 / 2.2.1: clarified that 7 days is the minimum washout period between Tub A and Tub B, not a fixed figure.

3. Dosing procedure (corrective action)

- Sections 1.1.2, 1.3.1 and 1.3.2: participants now receive one tub at a time. The investigator retains Tub B and issues it only when the participant is ready for the second dose, removing the possibility of unsupervised second-dose administration. Introduced following a deviation in which a participant self-administered Tub B unsupervised and missed the subsequent medical examination; their data has been excluded and reported to the DSMB, and the participants has been replaced.

- Section 1.3 (Schedule of Activities): "Issue a Tub to participant" now recorded as two separate events (Day 1 and Day 8), consistent with the above.
- Section 6.2: all capsule-size references standardised to Size 1 (correcting inconsistent references to "OO" capsules); denser 250mg-per-capsule packing for doses of 8g/day and above stated explicitly rather than simply being implied in the previous revisions.

4. Eligibility, screening and population

- Section 5.3: added Exclusion Criterion 7 (active condition identified at screening requiring treatment during the trial) and Exclusion Criterion 8 (allergy to dandelion or other Asteraceae/Compositae family plants, reflecting the placebo's dandelion root content); medication-allergy exclusion broadened to include food-plant allergies.
- Section 5.4: bilateral tubal ligation removed as a basis for non-childbearing-potential status. US exclusion reworded from a passport-based test to one matching the actual insurance exclusion: no participant who is a citizen or national of, domiciled in, or resident in, the United States, and no dosing or trial procedure while physically present in the United States.
- Section 5.6: screen failure clarified to include exclusion following review of pre-participation medical test results.
- Section 7.1: added specific discontinuation ground where pre-participation screening identifies a disqualifying condition, to remove any ambiguity on how that circumstance is processed.
- Section 8.4.1: added ultrasonography of liver and spleen for participants with SCD, and uterine ultrasonography alongside urine/blood testing for pregnancy where performed.
- Section 5.1 / 11.8: GDPR training confirmed explicitly for sub-investigators and data collectors.

5. Reporting and regulatory

- Section 9.2.3.1: removed the outstanding action to seek MHRA guidance on reporting format; reporting pathway to the Food Standards Agency and relevant national food safety authority, with precautionary MHRA notification, confirmed as settled.
- Section 11.1.1: updated the ISRCTN registration statement (previously referencing the superseded Rev A1) and added a statement confirming this amendment is being rolled out during the conduct of the trial without affecting Stage 1/Stage 2 data collected to date.
- Cover page: "Approximate Enrolled at Time of Sponsor Approval" restated to distinguish the proportion of the participant pool recruited and screened from the proportion of dosing stages completed.

6. Drafting corrections

- Glossary: ABR percentage corrected from 5% to 4.6%, consistent with the body text. "TDL" corrected to "TDI" throughout.
- Section 9.3.2: "Partner" replaced with "Wife or Girlfriend" following participant feedback that "partner" was unclear or had an unintended implication in two jurisdictions in which the Trial operates.

The Participant Information Leaflet (PIL) has been concurrently revised to Rev A2, principally to add a section explaining participant and Sponsor responsibilities where screening or medical examination identifies a previously unknown pre-existing condition, and to align monitoring, examination, and dosing descriptions with the changes above.

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1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

1.1.1 Primary and Secondary Objectives and Estimands

Refer to Section 3 Trial Objectives and Associated Estimands.

Trial Arm	Primary Objective	Secondary Objective
The Trial	To establish the maximum tolerable dose of African Bitter Root food Supplement (ABRS).	To identify any immediate side effects or tolerability issues.

1.1.2 Overall Design

Key aspects of the Trial design are summarised below.

Intervention:	ABRS-AR-200mg	Population Type:	Adult Volunteers
Intervention Model:	Double blind 3+3	Population Diagnosis or Condition:	Healthy users with the profiles observed to be consuming ABRS.
Control Type:	Double blind	Population Age:	Minimum: Age of majority or 18 years, whichever is the higher. Maximum: 90 years
Control Description:	50/50 Randomised cross-over.	Site Distribution and Geographic Scope:	Trial is run from the UK. No national restriction for participants other than excluding the USA.
Intervention Assignment Method	Double blind allocation.	Master Protocol:	3+3 Escalation and De-escalation.
Stratification	Not Applicable.		
Drug/Device Combination Product Indicator:	Not Applicable	Adaptive Trial Design:	Not applicable

1.1.2.1 Number of Arms: 1

The Trial has one arm.

1.1.2.2 Trial Blind Schema

Each cohort in the human trial is 3 participants, i.e. only 3 or two cohorts of 3 + 3.

At each dose escalation level, participants take either a placebo or ABRS assigned by double blind random allocation. For each participant at each dose level, after a washout period they switch to a second pack of the intervention. Either the first or the second is ABRS, but not both.

The schema includes provision for increasing the washout period when Tolerability-Limiting Events (TLEs) are reported during the placebo period.

1.1.2.3 Blinded Roles:

The following roles indicated will not be made aware of the treatment assignment, i.e. whether any dose is a placebo or ABRS, during the trial: All Participants, DSMB, Principal Investigator (PI) and anyone reporting to the PI including all sub-Investigators, data-collectors, translators or cultural liaison staff, data entry.

Additionally, the Sponsor's representative operates under blinded conditions in practice: all TLE processing and dose-escalation decisions are made by CT Manager, which does not expose blinding information and keeps the blinding and logs encrypted until the unencrypted export is produced at trial completion. The Sponsor's representative has no operational means of accessing blinding information during the trial. A residual theoretical risk exists in that the manufacturing randomisation files, though deleted after use, may in principle be recoverable (e.g. from a deleted-files store) and could allow the blinding to be inferred if deliberately sought. For this reason, the Sponsor's representative is not formally listed as a guaranteed-blinded role, notwithstanding that no unblinding occurs, and is not expected to occur, during the ordinary conduct of the trial.

The DSMB can request emergency unblinding in the event of a SAE. Emergency unblinding is logged automatically. There is no other unblinding possible until the trial has been completed: the program CT Manager that executes the schema will not accept any further data once a trial is completed.

1.1.2.4 Number of Participants:

The number of active participants at any one time is a minimum of 3 and a maximum of 6.

The dose is a modified Fibonacci sequence starting at 12g/day and a maximum of 25g/day. In the worst case, if the trial applies every increment all the way to 25g, with all 4 stages expanding to 6 participants, it would require 24 participants. In a more realistic scenario, 9 to 12 participants are likely to be required.

1.1.2.5 Duration:

Total planned duration of Trial participation for each participant: two days per dose level plus a washout period between the two doses (a minimum of 7 days with provision to increase to 14 days).

The actual washout period of ABRS is believed to be 24 hours, as the compounds present are dominated by lipids, fatty acids and sugars. Use of a minimum 7 day washout is used to prevent misallocation of residual AEs to placebo when they arise from ABRS.

1.1.3 Committees

Refer to Section 11.1, 11.2.

1.2 Trial Schema

The following section has been clarified since the Revision A0, and A1. There has been no change to the schema but opportunities for ambiguity are removed. The schema is expressed in narrative below that has been clarified, and a state machine description has been added which was used during the validation of the SPARK Ada implementation. All changes in this section are a result of the SPARK Ada validation process and are not an actual change to the original Rev A0 schema.

1.2.1 Trial Schema in English

The trial starts by enrolling participants, providing the PIL, answering any questions arising, ensuring the participant understands the PIL and obtaining consent on the ICF.

Once participants are enrolled by signing the ICF, they have a medical examination which includes laboratory tests. Their medical exam results are reviewed by the PI and their eligibility is either affirmed or they are discharged from the trial and a replacement is enrolled.

1. Trial

1.1 Assign a cohort of 3 participants from those who are enrolled, have passed screening, have had their medical examinations and for whom laboratory pre-participation results are available. A participant participates at only one dose level.

1.2 Assign intervention packs A and B to each participant; these are pre-randomised by the manufacturer as to which pack contains ABRS and which contains placebo.

1.3 Administer doses according to protocol, observed by the PI. Participant takes all of pack A, waits the washout period (initially a minimum of 7 days), then takes all of pack B. A data collector stays with the participant for the first hour to detect any early Tolerance-Limiting Events (TLEs).

1.4 Assess safety and record TLEs within the assessment window which is from the first dose (placebo or ABRS) to seven days after the second dose (placebo or ABRS). Safety is assessed by the PI. All TLE events are reported to the DSMB promptly.

1.5 The TLE assessment is performed by a SPARK Ada computer program which has the encrypted blinding information loaded, but not visible to users of the program. The program is given a serial number for the intervention packs and the day on which the TLE occurred (if any). It determines whether the reported TLE is on a day with the placebo or a day with the ABRS, for all 3 in the cohort (or 6), and recommends the escalation action.

The program uses the following algorithm on receipt of reports of TLEs. *This screening is invoked on reports received during the assessment window (before both packs are necessarily completed) to separate placebo TLEs from ABRS TLEs, to take early action.*

1.5.1 If the reported TLE is for a participant on the placebo who has not had ABRS then the program instructs the investigator to substitute that participant and run that same dosage with the new participant.
Clarification: This rule applies to early TLE reports during the first pack when it is identified as placebo.

1.5.2 If the reported TLE is for a participant whose last dose was ABRS, it is treated as a TLE.

1.5.3 If the reported TLE is for a participant who used the placebo for their last dose, but who has been exposed to ABRS at the dose for that stage previously, then the entire stage is repeated with the washout period increased to 14 days, and that increased period shall be used for the remainder of the trial.
Clarification: "Entire stage" means the current dose level's cohort evaluation. Current cohort data for this dose is reset; a fresh cohort of 3 is enrolled using the new 14-day washout. The 14-day washout applies to all future participants.

2. Apply 3+3 Decision at Current Dose

When: CT Manager, a SPARK Ada program encoded with this trial algorithm, processes TLEs as they are reported. If no TLEs are reported within 24 hours after second dose, then report no TLE to the program. If a TLE occurs later than 24 hours after last dose but within the observation period of 14 days, enter the TLE for the participant, in which case the program will reprocess the decision.

2.1 If 0 TLEs in the first 3 participants, escalate to the next higher dose with a new cohort of 3.

2.2 If 1 TLE in the first 3 participants, expand the cohort to 6 participants at the same dose.

2.3 If 2 or more TLEs in the first 3 participants, stop escalation and designate the previous lower dose as the MTI candidate.
Clarification: If this occurs at the entry dose (12 g/day) with no prior lower dose tested in this

trial, initiate de-escalation to the next lower dose in the predefined sequence and test a new cohort there using the same rules.

3. Expanded Cohort Review

3.1 Continue treatment and monitor safety for all 6 participants.

3.2 If total TLEs are 1 or fewer out of 6, escalate to the next dose.

3.3 If total TLEs are 2 or more out of 6, stop escalation and designate the previous lower dose as the MTI candidate.

4. Escalation Loop and Stopping

4.1 Repeat the dose-escalation steps for subsequent dose levels until a stopping rule is met or the highest planned dose is tested.

4.2 The dose is a modified Fibonacci sequence starting at 1 g/day and a maximum of 25 g/day, with the first dose entry point in the series at 12 g/day. *The complete ordered list of doses to be used is defined explicitly in the protocol (i.e: 1, 2, 4, 8, 12, 16, 20, 25 g/day). The series supports both escalation and de-escalation.*

5. Trial Completion Decision

5.1 If the highest planned dose is completed without TLE, CT Manager will select the highest tested dose as the MTI for further study.

5.2 If a stopping rule is triggered (a determined in Step 3), CT Manager will select the previous safe dose as the MTI for further study.
Clarification: If no safe previous dose has been established (toxicity at entry or lowest dose), the trial documents that no MTI was identified.

6. Close Trial

End the trial and document the selected dose and safety outcomes. All TLE attributions, program recommendations, washout changes, substitutions, and DSMB communications must be archived.

1.2.1.1 Additional Notes on Special Rules & Edge Cases (from TLE Processing)

1. **Multiple TLEs / same participant**: Rules applied per participant completion.
2. **Substitute vs full reset**: Substitute affects only one slot (keeps other participants' data); full repeat resets whole current stage/cohort.
3. **Washout increase timing**: Applies immediately to any new participation after trigger; current participants may have already used 7d (their data stands or reset per rule).
4. **Program output**: SPARK Ada recommends action (e.g., "Substitute participant X", "Repeat stage with 14d washout", "Count as valid TLE: total now Y", "Escalate to Stage 4 / Expand / Stop"). Investigator/PI executes; DSMB oversees.
5. **If TLE during washout or outside window**: Ignored per protocol (assessment window defined strictly).
6. **De-escalation from entry (12g)**: If ≥2 TLEs in first 3 at 12g, de-escalate to next lower (e.g. 8g) and test new cohort there using same rules. This resolves ambiguity where "previous lower dose" might not have been tested yet.
7. **Highest dose toxicity**: Treated as stop → MTI = previous safe (which could be 12g or whatever last passed).
8. **Withdrawal.** Where a participant withdraws after completing Tub A but before completing Tub B, the TLE algorithm cannot be executed for that participant; the withdrawal is processed in accord with Section 10.4.1.3. If this occurs, the participant should be replaced and no TLE recorded unless they report a TLE. Refer to Section 7.3 for detailed protocol for handling withdrawals.

1.2.2 Trial Schema as a Finite State Machine Model

The schema above is defined by a Finite State Machine (FSM) for use by the team verifying the correctness of its configuration in CT Manager (the SPARK Ada decision engine used for the trial). To avoid any ambiguity the FSM is definitive.

Concrete Dose Sequence

`[1, 2, 4, 8, 12, 16, 20, 25]` g/day
Entry point: 12 g/day. Supports both escalation and de-escalation.

States

Pre-Cohort - NotStarted - RecruitingParticipants - ScreeningAndMedicalExam - Enrolment - CohortAssignment

Dosing & Monitoring (Atomic) - AssignPacksAndRandomisation - DoseA_Observed (PI + data collector first hour) - MonitorPostDoseA (early TLE window) - WashoutPeriod (7 or 14 days) - DoseB_Observed - MonitorPostDoseB (full assessment window active) - AssessmentWindowActive - ReportNoTLE_At24h - LateTLE_Entered

TLE Processing (Separate States) - TLEReported - EvaluateRule1_5_1_Substitute - EvaluateRule1_5_2_CountAsTLE - EvaluateRule1_5_3_RepeatStage14d - ProcessLateTLE_ReprocessDecision - NoTLE_24h_Processed

Decision & Control Flow - CohortReadyForDecision - CTManagerApplyingDecision - Escalating - Deescalating - StoppingEscalation - CompletingAtHighest - Closed

Key Variables

`current_dose`, `previous_safe_dose`, `washout_days`, `cohort_target`, `num_tles`, `num_completed`, `dose_sequence`, `mti`, `late_tle_reprocess_flag`, `current_participant_dosing_phase`

Current State	Event / Condition	Actions	Next State	Notes
NotStarted	Trial start on approval + registration+MHRA notification, ethical case approved, DSMB in place.	Initialise CT Manager with encrypted blinding + algorithm; load dose list. Manufacturer issues all packs to PI, including for +3 cohorts, pre-randomised.	RecruitingParticipants	—
RecruitingParticipants	Potential participant presents	Provide PIL, answer questions, confirm understanding, sign ICF	ScreeningAndMedicalExam	—
ScreeningAndMedicalExam	ICF signed	Medical exam + labs performed	Enrolment	—
Enrolment	PI reviews results	Eligible → add to pool; Ineligible → discharge + replace	RecruitingParticipants or CohortAssignment	Replacement loop
CohortAssignment	≥3 eligible participants ready	Assign cohort of 3; each gets only this dose level	AssignPacksAndRandomisation	1.1
AssignPacksAndRandomisation	Cohort assigned	Manufacturer pre-randomised packs A/B assigned; blinding loaded in CT Manager	DoseA_Observed	1.2
DoseA_Observed	Dosing time for pack A	Audit check of documentary compliance, PI observes administration; data collector present first	MonitorPostDoseA	1.3 – observed + 1 h data collector

Current State	Event / Condition	Actions	Next State	Notes
		hour for early TLE detection		
MonitorPostDoseA	During/after Dose A (within assessment window)	Monitor for TLEs; any TLE → immediate report to PI+SR+CT Manager+DSMB	TLEReported or WashoutPeriod	Early TLE possible here
WashoutPeriod	Dose A completed, no early action taken	Participant waits washout (>=7 or 14 days per current setting)	DoseB_Observed	washout_days variable
DoseB_Observed	Washout complete; time for pack B	PI observes administration of pack B. If participant has withdrawn then participant should be replaced and participate from Dose A.	MonitorPostDoseB or DoseA_Observed	1.3
MonitorPostDoseB	After Dose B; assessment window continues until +7 d after B	Full safety monitoring; TLEs reported as they occur	TLEReported or AssessmentWindowActive	—
AssessmentWindowActive	Ongoing monitoring until end of window or decision point	Continue observation; TLEs routed to CT Manager in real time	TLEReported or ReportNoTLE_At24h	—
ReportNoTLE_At24h	Exactly 24 hours after last dose (B) and no TLE reported yet	CT Manager receives explicit “no TLE” signal for participant	NoTLE_24h_Processed	24 h trigger from narrative
LateTLE_Entered	TLE reported >24 h after last dose but still inside 14-day window	Record TLE; set `late_tle_reprocess_flag = true`	ProcessLateTLE_ReprocessDecision	Triggers reprocessing
TLEReported	Any TLE reported by PI (day + serial) during window	CT Manager receives report in real time; determine last dose type	EvaluateRule1_5_1_Substitute or EvaluateRule1_5_2_CountAsTLE or EvaluateRule1_5_3_RepeatStage14d	Real-time processing
EvaluateRule1_5_1_Substitute	TLE on placebo and participant has not yet had ABRS	Instruct substitution; enrol replacement; do not count TLE; preserve other data	MonitorPostDoseA or DoseB_Observed (replacement)	Exact 1.5.1
EvaluateRule1_5_2_CountAsTLE	Participant’s last dose was ABRS	Treat as valid TLE; `num_tles =+, If not flagged, flag` participant)	MonitorPostDoseB or CohortReadyForDecision	Exact 1.5.2 wording
EvaluateRule1_5_3_RepeatStage14d	TLE on placebo last dose + prior ABRS exposure at this dose	Reset current cohort data for this dose; set `washout_days = 14`; enrol fresh cohort of 3 with 14 d washout	CohortAssignment	“Entire stage” reset + 14 d for remainder

Current State	Event / Condition	Actions	Next State	Notes
NoTLE_24h_Processed	"no TLE" at 24 h processed	Record no TLE for participant; continue monitoring if needed	AssessmentWindowActive or CohortReadyForDecision	—
ProcessLateTLE_ReprocessDecision	Late TLE entered and flag set	Re-evaluate current cohort decision with updated `num_tles`	CohortReadyForDecision	Reprocessing per narrative
CohortReadyForDecision	All participants in cohort completed assessment or decision point reached	CT Manager finalises `num_tles` for the cohort	CTManagerApplyingDecision	—
CTManagerApplyingDecision	CT Manager evaluates 3+3 rules on current `num_tles` and `cohort_target`	0 TLEs (3) → escalate1 TLE (3) → expand to 6≥2 TLEs (3 or 6) → stop≤1 TLE (6) → escalate	Escalating or Deescalating or StoppingEscalation or CompletingAtHighest	CT Manager owns decision (real-time + reprocess capable)
Escalating	Decision = escalate and higher dose available	`previous_safe_dose = current_dose; current_dose = next`; reset counters; `cohort_target=3`	CohortAssignment	4.1
Deescalating	Stop triggered at entry dose with no prior safe dose tested	`current_dose = next lower` (e.g. 8 g); reset; new cohort	CohortAssignment	2.3 clarification + Note 6
StoppingEscalation	Stop decision (≥2 TLEs) or no safe previous dose	Set `mti = previous_safe_dose` or document "no MTI"; archive everything	Closed	5.2 + 6
CompletingAtHighest	Highest dose completed with zero TLEs (CT Manager confirmed)	Set `mti = current_dose` (highest tested)	Closed	5.1 exact "without TLE"
Closed	All documentation complete and archived	Trial ends	(Terminal state)	6

1.2.2.1 Implementation Notes for CT Manager (SPARK Ada) Validation

1. For the implementation in CT Manager, the FSM has precedence over the English narrative.
2. The English narrative is validated against the FSM.
3. Every TLE report (and the explicit 24 h "no TLE" message) is processed in real time by CT Manager. The trial activity log shall be exported from CT Manager at close of trial.
4. Late TLEs cause re-evaluation of the current cohort decision.

1.2.3 Participation schema

The participation schema is for each participant.

Enrolment. Inform with PIL ⇨ **MedExam and** ⇨ **Take first dose and monitor** ⇨ **7d** ⇨ **2nd Dose, monitor 24 hours.**

& written consent	**confirm eligibility**	**Record results and apply to program to determine TLE action.**

Figure 2: Participation Scheme

1.2.4 Dosage regimen

The dosage regimen uses a modified Fibonacci series with support for both dose escalation and de-escalation.

The initial dose starts with one step in the Fibonacci series above the largest dose observed to be in common use in the traditional setting, corrected for the purity of the components, and stops at the practical limit of consumption equal to 125 of the standard 200mg capsules per day.

That means, the initial dose is equal to 12g/day, maximum dose is equal to 25g/day, theoretical minimum dose with full de-escalation is equal to 1g/day.

To keep dosage within volume easily consumable by participants, i.e. 16 capsules taken at one time, a stronger percentage of ABR is used than in the reference 200mg 4.6% ABR formulation and the dose is packed to 250mg instead of 200mg in the same capsule for doses of 8g or more.

1.2.5 TLE Definition

A TLE is a Grade 1 symptomatic AE, or higher AE using CTCAE criteria, with plausible (i.e. possible) causality, or is any Unexpected AEs. This very low threshold is appropriate to a trial of a food product.

All AEs shall be assessed by the PI, who is a qualified clinician.

All AEs of any type shall be reported immediately to the DSMB and to the Sponsor, with their CTCAE classification and, as soon as it is available, the conclusion on causality. All AEs with plausible causality are ARs and shall be reported to the relevant food safety authority as stated in Section 9.2.3.1.

Food products are not normally expected to cause any ARs, whether taken for general health as a food supplementation or as a foodstuff.

If one participant has more than one TLE corresponding to one dose, only the first TLE is used to run the trial protocol algorithm but all TLEs shall be reported by the trial and to the DSMB.

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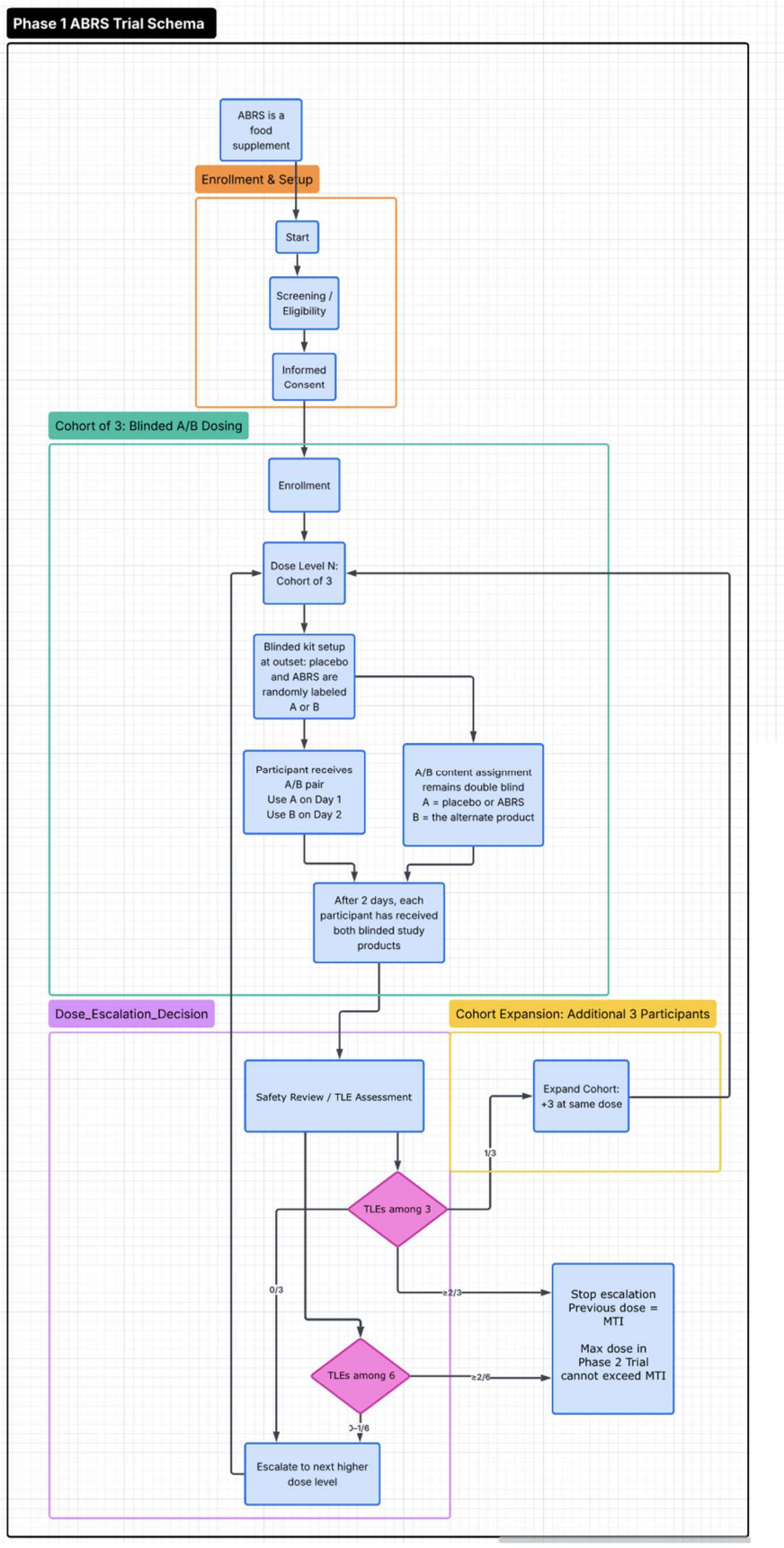

Figure 1: Trial Scheme to determine Maximum Tolerable Dose (MTI).

The algorithm used for the TLE assessment is given in the previous paragraph.

The sponsor has implemented this algorithm in a program written in SPARK Ada, that meets the requirements to IEC 61508:2010 at SIL3. The program acts as an independent statistician, given the serial numbers of the intervention given to each user it advises the outcome without unblinding.

The SPARK Ada program was developed in a Functional Safety process certified to meet SIL 3+, which requires verification independent of the author of the program. This is performed using SPARK assertions and Monte-Carlo testing. In this case the Monte-Carlo tests are exhaustive (100% coverage).

1.3 Schedule of Activities

Activity Timeline

Activity	Screening / Enrolment	Pre-dose Examination (Day -90 to 1)	Tub A Dose (Day 1)	30 min post Tub A	1 hour post Tub A	Day 2 (1 day post Tub A)	Day 8 (1 week post Tub A)	Tub B Dose (Day 8)	30 min post Tub B	1 hour post Tub B	Day 9 (1 day post Tub B) Post-dose Examination)	Day 15 (1 week post Tub B)
RECRUITMENT												
Confirm eligibility against inclusion / exclusion criteria	✓	✓										
Provide PIL and verbal explanation	✓											
Obtain written informed consent	✓											
Assign participant reference number	✓											
Record participant history on anonymised data form	✓											
Confirm re-eligibility (no acute illness since enrolment)	✓	✓										
CLINICAL EXAMINATIONS												
Physical examination (contracted clinic)		✓									✓	
Vital signs (BP, HR, temperature, respiratory rate)		✓									✓	
ECG		✓									✓	

Activity	Screening / Enrolment	Pre-dose Examination (Day -90 to 1)	Tub A Dose (Day 1)	30 min post Tub A	1 hour post Tub A	Day 2 (1 day post Tub A)	Day 8 (1 week post Tub A)	Tub B Dose (Day 8)	30 min post Tub B	1 hour post Tub B	Day 9 (1 day post Tub B) Post-dose Examination)	Day 15 (1 week post Tub B)
Haematology +biochemistry blood panel		✓									✓	
Ultrasonography, infective agent screening and other additional screening if initial screening finds anomaly indicating unknown risk, and for all persons with SCD.		✓									✓	
INTERVENTION												
Issue a Tub to participant			✓					✓				
Administer Tub A (self-dose, empty stomach, water) observed by investigator.			✓									
Administer Tub B (self-dose, empty stomach, water) observed by investigator.								✓				
MONITORING AND FEEDBACK												
Quantitative interview — pre-dose status		✓						✓				
Quantitative interview — 30 min post-dose				✓					✓			
Quantitative interview — 1 hour post-dose					✓					✓		
Quantitative interview 1 day post-dose						✓					✓	

Activity	Screening / Enrolment	Pre-dose Examination (Day -90 to 1)	Tub A Dose (Day 1)	30 min post Tub A	1 hour post Tub A	Day 2 (1 day post Tub A)	Day 8 (1 week post Tub A)	Tub B Dose (Day 8)	30 min post Tub B	1 hour post Tub B	Day 9 (1 day post Tub B) Post-dose Examination)	Day 15 (1 week post Tub B)
Quantitative interview 1 week post-dose							✓					✓
Record all feedback on data form	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓
ADVERSE EVENTS												
AE monitoring and recording throughout participation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Report all AEs promptly to PI and sponsor via Jira (eDMS)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Apply TLE assessment via SPARK Ada program											✓	✓
SAFETY AND ESCALATION												
Report all TLEs promptly to DSMB			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DSMB escalation / de-escalation decision		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WITHDRAWAL / EXIT												
Record reason for early exit (if participant willing)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Collect all available data on exit		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

1.3.1.1 Notes to Table

Tub A / Tub B assignment: Each participant receives one tub of ABRS and one tub of placebo, pre-randomised and blinded by the manufacturer. Tub A is taken first; Tub B is taken after the washout period. The participant is not informed which tub contains ABRS.

Washout period: The standard washout period between Tub A and Tub B is 7 days (Day 1 to Day 8). The trial schema includes provision to extend this to 14 days if TLEs are reported during the placebo period attributable to residual ABRS exposure, in which case Tub B is administered on Day 15 and the post-dose examination and final follow-up shift accordingly.

Pre-dose examination: Conducted at a clinic contracted by the trial before any dose from either Tub A or Tub B is taken, prior to administration of Tub A. Test results from accredited laboratories on samples taken up to 90 days before their participation, up to three months prior to actual participation may be accepted as being the Day 1 examination to avoid unnecessary duplication of invasive tests.

Tub A Dose: This shall be video recorded. The video shall be kept with the confidential file on USB stick marked private confidential information. Participation in the Tub A shall avoid if possible Saturdays or on days where the subsequent dose would fall on a day where the following day is closed for laboratory samples.

Tub B Dose: This shall be video recorded. This occurs 7 days after Dose A, that is, if Dose A is on Day 1, then Dose B is on Day 8 or later. The video shall be kept with the confidential file on USB stick marked private confidential information. Participation in the Tub B may be delayed by up to 3 days if it occurs on a day when the clinic or laboratory are closed for samples on the subsequent day. That is, the washout period can be extended to ensure that the medical tests following dose B is performed 24 hours after dosing.

Post-dose examination: Conducted at the contracted clinic one day after administration of Tub B, after the participant has received both blinded study products. As stated above, where the second dose falls on a Saturday, then the dose shall be postponed to the Sunday, to ensure the post-dose exam in carried out the day after the second dose participation.

Monitoring contacts: All monitoring interactions are by quantitative interview using the structured data form. Contacts may be in person, by telephone, or by secure VoIP (including Zoom or WhatsApp with security provisions described herein). All responses are documented and reviewed by the PI.

TLE assessment timing: The SPARK Ada program applies the TLE assessment algorithm at the end of each assessment window: Day 2 and Day 7 for Tub A, and Day 9 or Day 15. The assessment window runs from the first dose to seven days after the second dose. Within the program, no AE is recorded until an AE is entered. The program maintains a log of all interactions in a format that cannot be tampered: it is an encrypted file that only the program knows how to decrypt and export as an XML file.

Day 7 contact: This contact serves simultaneously as the one-week post-Tub A follow-up and the pre-dose interview for Tub B. The pre-dose clinical examination is not repeated at Day 7; it was conducted at Day 1. The Day 7 contact is a monitoring interview only.

1.3.2 Activity narrative

In narrative form, this timeline is:

Recruitment	Validate prospective participant's eligibility in accord with Section 5.2 and 5.3. Participants will be recruited from the pool of existing users of ABRS and of healthy volunteers. The trial does not replace or interfere with any care that the participant's clinical team can deliver. The trial is not presented as providing any therapeutic benefit. Explain the information in the PIL verbally and ensure prospective participant understands its contents, including the ability to leave the Trial at any time, without having to give any reason. If the prospective participant wishes to join the Trial, obtain their consent in writing on the written consent form and provide to the Principal Investigator for treatment as confidential personal data. All other reports shall be anonymised using the reference number on the consent form. Record the participant's relevant history and details on the data collection form: this is anonymised using the reference number on the consent form. Once enrolled, the medical exam including laboratory tests must be conducted. These are reviewed by the PI, before enrolment is approved. Once approved, they are called down as cohorts as each Stage starts.
Intervention	The PI must see each participant take each dose, either in person or over Zoom. An audit that all procedures have been followed correctly will immediately precede participation, including check with participant that PIL has been understood, ICF signed, any changes to any participant facing document is understood, the medical examination has been done, results have been reviewed and that no negative events have occurred since then. Provide Tub A of 16 capsules to participant (visually identical to the reference 200mg tablets, but packed to 250mg), in a pack with two tubs one of which is marked A and one is marked B. The participant receives only one tub at a time: the investigator keeps Tub B until the participant is ready for the second dose. Tub A must be used first, then B. Each tub contains one dose for that stage, of either placebo or ABRS. The initial dose is 12 grams (16 capsules) from Tub A. At no time may the dosage exceed 25 grams/day (16 capsules by increasing the percentage of ABR per capsule). Capsules may be swallowed whole, or the powder from the capsules emptied into a glass of water, and taken in liquid form. The capsules must be taken in front of an investigator. After quantitative interview to identify any signs of toxicity, the participant will be asked to take the same dose 7 days later from Tub B (7 days being the washout period). The trial schema includes provision to increase the washout period to 14 days. The Participant may choose to abandon the Trial or to continue with the Trial intervention at any time. Ensure the Participant has the phone number of both the PI and Sponsor contact, with instruction to contact the PI immediately if they have any adverse event, and certainly in the case of any life threatening situation.

	If the physical examination cannot be done 8 days after the first dose, for example, if it falls on a Sunday when the clinic is closed for samples, then delay the second dose until the clinic is open on the day following intervention.
Monitoring	Obtain feedback for each intervention dose, prior to intervention, 30 minutes after starting each intervention, an hour, 1 day and one week after. Two physical medical examinations will be performed, one pre-dose and one post-dose. In the context of these examinations, "Pre-dose" means before taking any dose from either Tub A or Tub B, and "post-dose" means after taking both Tub A and Tub B. The physical examination would be conducted one day after taking the second dose. Record all feedback and use the questions on the data form. For participants who left the Trial early, where the participant is willing to give information, determine the reason for Trial exit. A diary of all trial events is maintained by the PI, in addition to the recording by the CT Manager tool.
Exceptions	All AEs and exceptional events to be informed promptly to the Principal Investigator and to the Sponsor's Head of Compliance, who will advise what action to take.

2 INTRODUCTION

2.1 Purpose of Trial

ABRS has been used in the manner of a herbal food supplement in a group of remote communities in Nigeria since ancient times by persons with either sickle cell disease or osteoarthritis – two unrelated diseases other than their pathology involves impediments to cells slipping over each other freely.

ABRS is a nutraceutical with classification dependent on territory. It is classified as a herbal food supplement in the UK and Europe.

The sponsor has been distributing ABRS without any safety notices or complaints to date.

Dosage marked on the commercial package is 1 gram/day to 4g/day, based on observation of traditional use. This trial uses higher doses as per the trial schema: see Section 6.4.

The purpose of the Trial is to determine the safe dose of ABRS to inform the design of subsequent phased clinical trials planned to validate whether there is any health benefit to using ABRS.

2.2 Assessment of Risks and Benefits

2.2.1 Risk Summary and Mitigation Strategy

Toxicity

The manufacture of ABRS uses a HACCP in accord with Good Manufacturing Practice in the food industry.

No formal toxicology studies (acute, repeat-dose, genotoxicity) are available as the whole product is a food with a long history of substantial use: food supplements are dietary nutritional supplements. This is typical of a herbal food supplement.

Safety has been assessed by the manufacturer observing tradition use, where it has been in substantial use for many generations, and by laboratory testing. The manufacturer has performed HPLC and GC-MS

analyses using methanol, HPLC water and hexane solvents, then comparing each component against TDI limits published by the EFA and against published NOELs. The manufacturer has analysed the effects of exposure to stomach acid by GC-MS analysis following 30 minutes exposure to 0.01M of hydrochloric acid.

The full identity of the plant (scientific name and genus), along with the HPLC+GC-MS data is in a confidential master dossier[1] maintained by the manufacturer. The dossier includes details of the SOPs and QA measures which implement food grade GMP. This data has been provided to the PI and is available to the DSMB under NDA limiting use of that data to safety assessment for the purposes of this trial.

It is recognised that food grade GMP differs materially from pharmaceutical GMP (Annex 13 IMP GMP). The manufacturer's GMP is in fact much better than food grade GMP as it is based on its medical device production; the manufacturer is ISO 13485:2016 certified and its GMP reflects medical grade GMP. However, it is not a pharma certified GMP.

The ABR root bark contains natural lipids and fatty acids. The dried root bark is combined with 95% mass fraction of kaolin (a natural clay mineral) and a small amount of salt (Sodium chloride 0.4%). The large mass fraction of kaolin acts as a pH buffer and as a high surface area mineral matrix carrier, distributing the lipids and fatty acids in a molecule-thick layer on its surface. The salt helps keep the kaolin as an emulsion when combined with water and establishes the correct zeta potential so the kaolin can release the lipids effectively. This combination forms a rapid delivery vehicle allowing the lipids to pass rapidly from the stomach to the small intestine, where they are absorbed quickly through the villi into the lymphatic system. The pH buffer action has been validated by the manufacturer performing GC-MS analysis using HPLC water as the solvent, before and after 30 minutes of ABRS exposure to a 0.01M solution of hydrochloric acid.

Doses of kaolin over 25.9 grams/day are considered an overdose based on the lowest toxic limit of 370mg/kg for Kaolin reported by CDC (IJNUB7 92,9,1997 and JONUAI 107,2020,1997)[2]. At Stage 1 (12g/day of standard ABRS containing 95% kaolin), the kaolin dose is approximately 11.4g/day — well within limits. However at Stage 4 (25g/day), if the standard formulation were used, kaolin would be 23.75g/day, which is close to but still within the 25.9g/day TDI limit. The protocol increases the safety margin by increasing the ABR percentage and reducing kaolin at higher stages. The table in Section 6.4 shows that at Stage 4 the ABR percentage is 28.68%, meaning kaolin is approximately 70.9% of the capsule content, giving approximately 17.7g/day of kaolin at 25g/day total dose. This is well within limits.

The Master Dossier contains case studies observing use in healthy users, and users with sickle cell disease, osteoarthritis or non-emergency pain, in the traditional setting, with no adverse effects.

In the case of ABRS, an exceptionally detailed toxicity study (for a herbal), has been performed, using analytical methods to identify each compound in the herb using HPLC and GC-MS with a spectrum of solvents. This detailed analysis is not available for almost any other herb: very few herbs have more than a single GS-MS result published, using a single solvent, which often contains contaminants and methylation products.

Identifying the active component in a herbal supplement is a complex process because herbs generally contain multiple active compounds and nutritional or beneficial effects often result from synergistic

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1 ABRS Master Dossier , in directory ABRS Master Dossier on SVN project repository, as of 10th December 2025.

2 CDC NIOSH Registry of Toxic Effects of Chemical Substances (RTECS), RTECS GF1670500, Updated Dec 2018, https://www.cdc.gov/niosh-rtecs/GF197D64.html Citing Oral dose of 370mg/kg reported to have toxic effects in rats, from Journal of Nutrition. (Subscription Dept., 9650 Rockville Pike, Bethesda, MD 20014) V.1- 1928.

interactions among various compounds rather than a single molecule. While isolation of specific active ingredients is possible, it is a lengthy and exhaustive process requiring extensive laboratory testing, and no single standard procedure exists for all herbs. That process is underway at the time of this trial design but is incomplete. Multiple analyses have been carried out for ABRS, including HPLC, and GC-MS with methanol, hexane and HPLC water as the solvents. The PI examined that safety analysis which is contained within the Master Dossier.

Method of Calculation of Dose of Each Compound

Conversion from GC-MS area volume results to mg/kg results was performed :

- drying the filtered solvent used to carry the sample (1g was used in each case),
- measuring the weight of Total Dried Solids (TDS),
- multiplying that weight by the area fraction and dividing it by the TDS weight
- multiplied by 0.046 to represent the concentration of ABR in ABRS
- multiply by 25 for a 25g dose by a 70kg adult.

GC-MS Results

In the analyses listed below, the Total Dried Solid weights of the extracted compounds from a 1g sample were:

Sample ID	TDS (g)	TDS (%)	Divisor to convert % area to g of ABRS	Remarks
ABRS in Water	0.0349	3.49	28.653	Slightly viscous
ABR in Water	0.2329	23.29	93.34	Viscous on drying
ABR in Methanol	0.1515	15.5	6.6	Not viscous
ABR in Hexane	0.0662	6.62	426.3	Viscous on drying

The extracted compounds identified by GC-MS that are present in the plant are:

Lipids, FAMEs, free fatty acids & derivatives (monopalmitin ~47 mg, linoleoyl chloride ~58 mg, methyl stearate ~21 mg, oleic/trans-13-octadecenoic acids ~13–17 mg each, phytol ~19.5 mg, etc.)

1. **TDI**: None established (GRAS / normal dietary fats).
2. **NOAEL**: >>1 000–5,000 mg/kg/day (essential fatty acids, monoglycerides, phytol read-across ~333 mg/kg/day).
3. **Margin**: >100–1,000× for every listed compound. These are normal components of vegetable oils and cell membranes. Daily dietary intake of similar lipids is often grams/day. Completely safe at these levels.

Sugars & sugar derivatives (1,5-anhydroglucitol ~20.3 mg, melezitose, etc.)

1. **TDI/NOAEL**: Not applicable (natural metabolites / food components).
2. **Margin**: Extremely large. No toxicity concern.

Phenolics / phenylpropanoids (ferulic acid ~14.2 mg, 2-methoxy-4-vinylphenol ~21.3 mg, syringol derivative ~16.6 mg, methyl salicylate, vanillin lactoside, etc.)

1. **TDI**: None established (common in fruits/vegetables).
2. **NOAEL** (ferulic acid example): ≥2,000 mg/kg/day.
3. **Margin**: >100–500×. Ferulic acid and related compounds are antioxidant food additives with excellent safety profiles.

5-Hydroxymethylfurfural (HMF) (total ~18.8 mg from two peaks)

1. **TDI**: None established (Maillard reaction product in cooked foods, unlikely to be actually present in sample).
2. **NOAEL**: 80–100 mg/kg/day (5,600–7,000 mg/day for 70 kg adult).
3. **Margin**: >300×. Normal dietary intake 4–30 mg/day (up to 350 mg from some foods). No relevance for carcinogenicity/genotoxicity at these levels.

Terpenoids / triterpenoids (phytol 19.5 mg, oleanane hexol 2.93 mg)

1. **TDI**: None.
2. **NOAEL**: Phytol ~333 mg/kg/day; triterpene saponins generally >500–1,000 mg/kg/day.
3. **Margin**: >100×.

Miscellaneous / minor (Dasycarpidan acetate ~5.8 mg, various furanones, 1-octanol 2-butyl-, aconitic acid, etc.)

1. **TDI/NOAEL**: No specific values; all occur at trace levels or are common plant volatiles.
2. **Margin**: Extremely large. No safety issues identified.

Contaminants from the measurement system and spurious results

Siloxanes, octane, 1-Octanol, 2-butyl- were present in the methanol GC-MS results: these were concluded to be contaminants from the GC-MS columns and seals.

Bis(2-ethylhexyl) (DEHP) phthalate was present. This was considered in detail, and is discussed below.

Trace digitoxin and an antibiotic not of plant origin (paromomycin) were present in the water GC-MS results. These artefacts were traced to library misallocation, as digitoxin is only mildly soluble in water and did not appear in the hexane or methanol results, nor did the antibiotic.

Some of the compounds identified in the GC-MS using methanol as the solvent analysis are the result of methylation, upon the sample being heated at the input port of the measurement equipment. The precursor to each of these compounds, i.e. before methylation, is not toxic (FAMEs).

Some compounds identified are a Maillard reaction between amino acids and sugars, e.g. Furaneol at 115mg in a 25g dose, and 5-Hydroxymethylfurfural at 18.8mg in a 25g dose. These compounds are not present in the sample but are products of heating in the GC-MS inlet port.

DEHP

DEHP and similar phthalate esters are synthetic compounds which are not biosynthesised by plants. Despite this, phthalate contamination of herbal and botanical products is well-documented. It occurs through environmental soil contamination (from agricultural plastics such as irrigation tubing), plastic packaging and processing equipment, and migration from capsule shells or storage containers. Kaolin, which constitutes 95% of the formulation, is an extracted mineral and can carry trace contaminants depending on its source and processing. The MHRA, EFA and EMA have all issued guidance on phthalate contamination in herbal medicinal products.

DEHP is also a known column bleed contaminant in GC-MS analysis, and its appearance in trace amounts in a chromatogram can genuinely reflect instrument contamination rather than sample composition. The samples were stored in food grade freezer bags following freeze drying: the sample bags were found to contain phthalates. These are not used for normal product, which has glass and stainless steel storage for frozen ABR.

The true level of phthalates in ABRS, was determined by GC-MS calibration runs after exclusion of storage bag source. There are some residual phthalates in the ABR. The levels concluded are a third of the limits set by the MHRA and EMA in guidance on phthalate contamination, and the TDI set by the EPA for foodstuffs, for a 25g/day dose of ABRS.

The phthalates are being monitored on a batch to batch basis by the manufacturer, with strict controls to eliminate all contact between the product and plastics, other than the use of MDPE irrigation pipe.

Margin of Safety for a 25g dose taken by a 70kg adult

The exposure to each of these compounds in this Trial is well below the Tolerable Daily Intake (TDI) levels set by the European Food Agency. This has enabled ABRS to be sold as a food supplement in the UK and Europe.

Margin of Safety (MOS) of a 70kg adult taking a 25 gram dose of ABRS.

Compound	Exposure (mg/kg)	TDI / NOAEL	Margin of Safety
Undecane	1.08	NOAEL ≥1000	>1000×
Phytol	0.575	NOAEL ≥1000	>2000×
Phthalate (DEHP)	0.016	TDI 0.05mg/kg, NOAEL 4.8mg/kg	3.125x (TDI) after removing measurement contaminants 300x (NOAEL)
Fats & Fatty esters	~0.5	dietary	effectively infinite
Flavonoids	<0.2	dietary	effectively infinite

Trial Intervention

In this trial participants are excluded if they have a disease in an acute phase. This excludes participants who are undergoing treatment with compounds that may mask toxicity including blood transfusions, opioid analgesics, or any other treatment for an acute disease as the use of ABRS in those circumstances may introduce additional risks to the participant, or which may mask AEs.

Populations at higher risk of the consequences of adverse reaction, including minors and pregnant women, are excluded.

The intervention, ABRS, has been in significant use as a food supplement and as a traditional Nigerian medicine for many generations. No safety concerns have been identified from observations of its indigenous use or during interviews with users.

The preclinical Trial did not identify any risks in the use of ABRS, other than in overdose, where the kaolin component causes constipation. Overdose is not possible during the trial because the participants are issued only the dose required.

The active components suspected to be in the African Bitter Root are highly soluble in aqueous solution, leading to rapid washout through renal channels, so any negative interaction should resolve within 24 hours. In this study, a seven day minimum washout is used between doses to avoid risk of any residual AE being misclassified.

Trial Procedures

The Trial procedures are a classic 3+3 Phase 1 trial, with double blinding.

The trial starts with the top end of the dose range user groups are observed to be using when taking the food supplement.

The period of intervention is the minimum: each participant only receives one dose of ABRS.

2.2.2 Benefit Summary & Background

Most herbals are treated as food supplements in the UK, as evidence of therapeutic benefit is either lacking or too weak to sustain the process required to register a medicine, either traditional or modern.

Herbal food supplements or nutraceuticals are widely distributed in the UK and Europe. They are controlled by regulations that govern foodstuffs. Those regulations do not require clinical trials or phased trials. The safety requirements in those regulations are fulfilled by the manufacturer of ABRS.

Most herbal food supplements are used by people with medical conditions. For example, the oldest herbalist in Scotland, Napier Herbals, has a web site listing many products with indications of what health

condition users have who are buying that food supplement. This is true of most herbalist sites in Europe. Each user group has anecdotal information suggesting a benefit, but in most cases, there is a paucity or absence of scientific evidence.

ABRS is classified as a food supplement in the UK and Europe.

ABRS is used by people with sickle cell disease and those with osteoarthritis, two apparently unrelated conditions. The manufacturer claims it to have cell membrane rejuvenation properties, based on biochemical analysis and in vitro tests; a claim not dissimilar to that made by some beauty treatments.

There have been no registered or published clinical trials of ABRS that indicate any therapeutic benefit.

For these reasons, the intervention is not an Interventional Medicinal Product within the meaning of UK and European regulations.

This trial seeks to establish a safe dose range for the food supplement, to inform future Phase 2 trials to explore whether there is any scientific evidence of health benefit associated with consuming ABRS.

In the event of scientific evidence being found in a Phase 2 or 3 trial of therapeutic benefit, all documentation is being maintained in formats that would support MHRA approval of the continuance of the trials and marketing approval of therapeutic versions of the product.

2.2.3 Overall Risk-Benefit Assessment

The risk-benefit balance of this Trial is one of establishing basic safety data to protect the public, and to provide the dosage data needed for Phase 2 trial to determine if there are any measurable benefits to its use.

3 TRIAL OBJECTIVES AND ASSOCIATED ESTIMANDS

3.1 Primary Objective(s) and Associated Estimand(s)

3.1.1 Primary Objectives

The overall primary objective is to obtain data on safety and dosage to enable Phased Clinical Trials to be conducted which will quantify the efficacy of the intervention. The table below describes how this primary objective is applied.

Table 1: Primary Objectives

Human	Establish the Maximum Tolerable Dose (MTI) of ABRS using a 3+3 algorithm, that includes double blinding to separate placebo effects.

This is a 3+3 Phase 1 trial, using established statistical methods.

Table 2: Estimands for the Primary Objectives

Estimand Characteristic	Description
Population	Adult participants from both sexes are included. Vulnerable groups are excluded, as are minors, pregnant women and women of childbearing potential who are not using contraceptives.

Treatment / Exposure	There is no treatment because the trial is not of an IMP. The exposure is use of the African Bitter Root Supplement. The dosage regime starts at 12g/day which is one step in the modified Fibonacci sequence above that observed in regular use in the indigenous setting, corrected for the purity (the substitution of the BP grade components for the native materials).
Endpoint	The endpoint for each participant is one week after commencing the intervention: this is sufficient exposure to determine whether the ABRS causes a TLE.
Population-level Summary	The Trial is measured by counting TLEs.
Other Intercurrent Event	Not applicable

3.2 Secondary Objective(s) and Associated Estimand(s)

3.2.1 Secondary Objective

Table 2: Secondary Objectives

Trial Arm	Secondary Objective
The Trial	Identify side effects or any safety issues.

Estimands are the same as for the primary objectives.

3.3 Exploratory Objective(s)

Data on the ethnicity of users will be collected.

4 TRIAL DESIGN

4.1 Description of Trial Design

The Trial uses a 3+3 escalation / de-escalation trial, with double blinding.

Participants receive the intervention sequentially. Sequential intervention is chosen to minimise risk of adverse effects. The Trial will be reassessed if any serious adverse effect is observed in any participant, as the preclinical observational Trial found no side effects.

The dose is equivalent to that observed to be used by indigenous population in each user group, corrected for the pure BP grade formulation instead of traditional Nigerian kaolin and rock salt.

The duration of participation is as short as possible consistent with obtaining the data in support or refute of the primary objectives. Each participant receives only one dose. The participation durations and schema are listed in Section 1.

The data collected with be available to both the investigators and the sponsors, with information identifying the participants held in a secure area of the SVN site accessible to the IT administrator and the Principal Investigator only.

4.1.1 Stakeholder Input into Design

The Trial has been designed by the Principal Investigator. Sponsor provided the technical framework including the QA and use of a SPARK Ada program .

There has been no public input to the design.

The trial has been informed by a prior observational study of users, in which one of the Sponsor's staff was the Principal Investigator.

4.2 Rationale for Trial Design

The Trial design is intended to be the simplest route to collect the data required to meet the Trial objectives.

While this trial is not of an IMP, aspects of IMP trials are informative to the design and conduct of this trial. The following Clinical Practice Guidelines were considered in the Trial design:

CARE Guidelines for Case Reports, 2013[3].

Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups.

STROBE: Observational Studies[4].

4.2.1 Rationale for Estimand(s)

The MTI and the washout period along with the effect of possible overdoses is critically important data needed to confirm the design of the subsequent Phased Trials on measuring any health benefit.

4.2.2 Rationale for Intervention Model

The intervention model is that of a well established trial scheme, featuring the lowest number of participants in an accepted trial protocol for Phase 1 dose escalation studies.

The MTI design is used not because ABRS is expected to have a toxic dose within the range tested, but because the 3+3 design provides the most statistically rigorous and participant-efficient method for confirming safety across a dose range that has not previously been formally characterised, and because the design's stopping rules protect participants if any unexpected effect does occur.

4.2.3 Rationale for Control Type

The trial involves ingesting large numbers of tablets: 16 capsules. This may cause false TLEs, so a placebo is included as a double blind layer over the entire trial. The control is the placebo usage.

A cross-over is used to identify weaknesses in the washout period, with binary logarithmic increases in washout period in the event of TLEs being reported for placebo use.

4.2.4 Rationale for Trial Duration

The duration is determined by the dose increment. The increment is determined using a modified Fibonacci series. In the worst case, the increment would give 4 stages, which in the worst case, involves 4x6 = 24 participants.

4.2.5 Rationale for Adaptive or Novel Trial Design

Not applicable.

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[3] CARE Guidelines published on https://www.care-statement.org/ and checklist https://www.care-statement.org/checklist

[4] STROBE, STrengthening the Reporting of OBservational studies in Epidemiology. Www.Strobe-statement.org

4.2.6 Rationale for Interim Analysis

Not applicable.

4.2.7 Rationale for Other Trial Design Aspects

Not applicable.

4.3 Trial Stopping Rules

Stopping rules are embedded in the trial schema.

4.4 Start of Trial and End of Trial

The Trial has been registered with ISRCTN prior to enrolment starting: ISRCTN Registration number, ISRCTN51184184

The Trial shall start when the ICF is signed by the first participant.

The Trial shall finish when the MTI has been determined.

4.5 Access to Trial Intervention After End of Trial

Participants may purchase the intervention at their own cost following the conclusion of the Trial, as it will be available as a food supplement in the UK, Europe and Australia.

5 TRIAL POPULATION

5.1 Description of Trial Population and Rationale

The trial population is drawn from the population likely to benefit from this trial, namely existing users of ABRS, supplemented by healthy volunteers. This trial does not examine or measure efficacy, only the tolerable dosage and safety.

One cohort of 3 participants in each stage, will be in Europe, and a different cohort will be in Africa. There will be no communication between the two groups, other than through the PI's data collection channel. The PI will appoint sub-investigators with purely a data collection role to each centre, following appropriate GDPR and protocol training.

5.2 Inclusion Criteria

To be eligible to participate in this Trial, an individual must meet all the following criteria at the time of joining the Trial, in addition to not meeting any of the Exclusion criteria:

1. Literate, able to understand the PIL, Consent and Reporting forms provided,
2. Have the capacity to make an informed decision without pressure,
3. Be over the age of 18 or the age of majority, whichever is the higher, and under the age of 90,
4. Be willing to participate in the Trial and report,
5. Free of any acute health issue requiring treatment during the participation period,
6. If a participant is of childbearing potential, it shall be confirmed that the participant is on a long acting reversible contraception (LARC) or another form of reliable contraception.

5.3 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this Trial if they do not meet the inclusion criteria above, or are:

1. Minors meaning any person under the age of 18 or under the age of majority, whichever is the highest.
2. With any drug dependency.
3. In a vulnerable population (unable to give informed consent, prisoners etc).
4. Pregnant women.
5. Having known allergies to medication or to food plants.
6. The PI's professional liability insurance excludes the USA. Accordingly, no participants may be enrolled who are citizens or nationals of, domiciled in, or resident in, the United States, and no participant may be dosed or undergo any trial procedure while physically present in the United States.
7. Having active conditions identified during the pre-participation screening that require treatment during the time period of the trial.
8. Known allergy to dandelion (*Taraxacum officinale*) or other plants of the Asteraceae (Compositae) family.

5.4 Contraception

5.4.1 Definitions Related to Childbearing Potential

1. A participant is considered to be of childbearing potential if the participant is female and has menstrual cycles.
2. Females who do not have menstrual cycles, whether through age, nutritional insufficiency, hysterectomy, are considered to be of non-childbearing potential for the purposes of this Trial.
3. All male participants are of non-childbearing potential by definition.

References to male and female are applied on the basis of biological sex.

5.4.2 Contraception Requirements

The packaging of ABRS as a food supplement states that it must not be used in pregnancy. This is a standard exclusion. The manufacturer has no data indicating any harm occurs in pregnancy, but recommends this exclusion for reason of safety.

It shall be confirmed that all participants of childbearing potential are on a long acting reversible contraception (LARC) or another reliable form of contraception, confirmed by question on enrolment.

The PIL states that ABR must not be used in pregnancy or if there is a possibility of pregnancy.

For women of child bearing potential, the physical examinations will include a pregnancy test.

5.5 Lifestyle Restrictions

5.5.1 Meals and Dietary Restrictions

Participants are asked to take the dose of the intervention with water on an empty stomach at least an hour before a meal.

5.5.2 Caffeine, Alcohol, Tobacco, and Other Restrictions

There are no restrictions on the intake of caffeine, alcohol, or tobacco.

5.5.3 Physical Activity Restrictions

There are no restrictions on physical activity.

5.5.4 Other Activity Restrictions

There are no other restrictions on activity.

The intervention does not induce drowsiness.

5.6 Screen Failure and Re-screening

The trial includes a pre-participation and post-participation medical examination, including taking appropriate medical history using a standardised form, medical interview, vital signs, ECG, FBC, Blood Panel, Urine Analysis, and for women with any possibility of pregnancy, a pregnancy test.

Participants with SCD shall be healthy and have ultrasonography of their spleen and liver additionally, and must not be in an acute SCD crisis or taking any medication other than vitamins (e.g. Folic acid and B12).

The PI shall review those results prior to participation. The PIL was amended on 6th July 2026 to cover use of those medical test results, to avoid any ambiguity over who is responsible for what, and what is done with the results.

Participants may be excluded from the trial if pre-participation screening indicates ineligibility, e.g. drug dependence, pregnancy or another condition with enhanced risk such as substantial liver or kidney disfunction.

Where screening failure occurs, it will be assessed by the Principal Investigator on a case by case basis.

6 TRIAL INTERVENTION AND CONCOMITANT THERAPY

Arm Name	Arm Type	Intervention Name	Intervention Type	Pharmaceutical Dose Form	Dosage Strength(s)	Dosage Level (g/day)	Route of Administration	Regimen, Treatment Period	Use	IMP/NIMP	Sourcing
The Trial	Clinical	African Bitter Root Supplement	Oral dose followed by observation	Gel capsule size 1.	4.6% ABR up to 4g, then increasing in ABR% to a maximum of 28.68%, equal to 25g of standard ABRS	1, 4, 8, 12, 16, 20, 25, with bulk reduced by increasing ABR % to limit dose to 16 capsules	Oral, equal to the reference commercial 200mg capsules but from 8g dose packed to 250mg to keep number of tablets per dose at 16.	Modified Fibonacci, single dose.	Any	N/A	Sponsor supplied: Deep Life Medical Ltd
IMP=Investigational Medicinal Product; NIMP=Not Investigational Medial Product; N/A=Not Applicable, for a foodstuff											

6.1 Description of Investigational Trial Intervention

The intervention is African Bitter Root Supplement (ABRS). This is traditional herbal medicine, categorised as a herbal food supplement in the UK and Europe.

ABRS has been in substantial use for many generations in communities in South East Nigeria. It is manufactured in the UK since January 2026 and distributed commercially as a herbal food supplement.

ABRS comprises 4.6% of African Bitter Root (ABR), which is the dried root bark of a native West African plant. No part of the plant has any known toxicity. The fruit of the plant is eaten as a food. The remainder is BP kaolin (95%) and salt (Sodium chloride 0.4%).

In this trial the proportion of ABR is increased, reducing kaolin, to keep the dose escalation to a limit of 16 capsules a day, which is a reasonable practical limit for ingesting Size 1 capsules. The packing is also increased from 200mg to 250mg per capsule.

The full identity of the ABR plant is in the manufacturer's confidential Master Dossier, which the PI has examined.

6.2 Rationale for Investigational Trial Intervention Dose and Regimen

The rationale for the trial design is stated in Section 4.1

The intervention is normally delivered in the form of 200mg capsules, Size 1 capsules (19.4mm long, 6.9mm nominal diameter) Each capsule normally weighs 260g including the gel capsule, but the packing is increased in this trial to 250mg, giving an overall capsule weight of 310mg. All doses in this trial are of weights that exclude the capsule body.

The capsules are in a heat-sealed PE tub with screw lid. A silica gel sachet is included in each tub to minimise humidity. No child-proof mechanism is on the lid, as some users are mobility impaired. The labelling states it must be kept away from children and must not be taken in pregnancy.

The dosage regime starts at 12g/day which is one step in the modified Fibonacci sequence above that observed in regular use in the indigenous setting, corrected for the purity (the substitution of the BP grade components for the native materials), and escalates to a maximum of 25g/day which is the practical limit for consumption. The modified Fibonacci sequence supports regression back to 1g/day which is one capsule above the lowest dose observed to be in routine use as a food supplement.

Doses over the range of 0.4g–25g have been observed in traditional use without reported adverse effects, and the GC-MS toxicity analysis covers the full 25g dose level. A person could take up to 25g/day so the study will determine if there are any negative effects from doing this. If so, a warning of this will need to be added to the product label.

The sponsor is not expecting any AEs to occur at any dose in this trial because the intervention is a foodstuff. The sponsor is aware of one person who consumed the equivalent of 32 grams of ABRS at one time, with no adverse effects, by dissolving ABRS in water, with a much higher concentration of ABR than usual. No AE was experienced by that person. The 25g limit is difficult for a person to exceed physically using the normal 4.6% concentration of ABR in ABRS, so is the appropriate upper limit for this trial.

Before any Phase 2 trial can be contemplated, the scientific evidence is required that the dose in in that trial is less than the maximum tolerable daily intake, which is the data this trial is designed to provide.

The lowest dose observed in traditional use is 0.4g/day which is two of the standard capsules. A more typical dose is 0.8g/day, which is two capsules taken twice a day. The standard commercial ABRS capsules contain 4.6% dried ABR by weight, with 0.4% of sodium chloride and BP kaolin making up the remainder.

25g/day of the commercial ABRS 200mg/capsule product would be 125 capsules. This is impractical for consumption, so for the 8, 12, 16, 20 and 25g doses, the 200mg capsules are packed at higher density to give a dose per capsule of 250mg in weight and use a percentage of ABR in ABRS that is increased in stages for the purposes of this trial up to a maximum of 28.68%, reducing the kaolin proportionately, to maintain the number of capsules consumed at not more than 16 per day.

The manufacturer supports the trial with free issue of the product, and labels the tubs of capsules with the stage number and total dose.

This increase in ABR percentage may affect the rate of absorption of supplement, as the manufacturer claims the kaolin provides a large surface area mineral matrix carrier, that enables the lipids in ABR to be absorbed rapidly (within 30 minutes). The effect of decreasing the kaolin content relative to the ABR, may cause an increase in absorption times. In extremis, the increase could be from 30 minutes with the standard formulation to 4 hours, the time for the GI to fully absorb lipids.

6.3 Investigational Trial Intervention Administration

Participants take the dose in front of an investigator on an empty stomach at least an hour before a meal this is the worst case for rapid absorption and hence create peak blood level of the constituent compounds.

Missed or delayed doses should not occur as only one dose is taken by each participant (one of the ABRS, and one of the placebo).

6.4 Investigational Trial Intervention Dose Modification

A Fibonacci sequence increases the dose in larger percentage steps at low dose levels and then gradually reduces the increase ratio as it approaches the maximum dose. A modified Fibonacci sequence is used :

Stage	Genuine Fibonacci	Modified Fibonacci	Increase ratio	ABR %	Capsules /day	Equivalent grams ABRS when packed to 200mg / cap	Equivalent grams ABRS packed to 250mg per capsule, 16 capsules
-3	1	1	-	4.6	5	1	
-2	2	4	4.00	4.6	20	4	
-1	3	8	2.00	9.2	16		8
1	8	12	1.5	13.8	16		12
2	13	16	1.33	18.35	16		16
3	21	20	1.25	22.94	16		20
4	34	25	1.25	28.68	16		25

Note that to provide the higher doses, within a reasonably comfortable number of capsules, a greater packing density is used for the 8, 12, 16, 20 and 25 doses, namely 250mg instead of 200mg, in the same capsule. This is achieved in manufacturing by increases the number of press cycles. The number of capsules these enhanced doses are equivalent to in standard 4.6% capsules, is tabulated below:

Stage	ABR %	Number of standard 4.6% capsules req'd	Number of enhanced 200mg / caps required	Number of enhanced 250mg/caps
-3	4.6	5	1	
-2	4.6	20	4	
-1	9.2	40		8
1	13.8	60		12
2	18.35	80		16
3	22.94	100		20
4	28.68	125		25

The first step in the sequence is a x4 increment, followed by a x2 increment, to cover the range of typical doses observed to be used by traditional users, none of whom report any AEs, without the need for unnecessary stages. As the dose rises to above the level observed in common use, the Fibonacci series converges to asymptotic increase ratio of 1.25:1.

The dose in the series starts at 1g/day which is one capsule above the lowest standard dose recommended by the manufacturer, based on its observations of traditional use. Common dose levels in indigenous use are from 0.4g to 8g/day. The dose of 25g/day is known to have been taken by one traditional user during an SCD crisis without adverse effects, and one OA user has taken 32g at one time using a concentrated formulation of ABRS. No user has been observed to have any adverse effects attributable to ABRS.

As there is substantial observational use of doses up to 8g/day, the trial will commence with the first dose that is in the series that is above the common observational use level, i.e. the trial will commence with a dose of 12g/day. This as an application of the ethical principle of not exposing participants unnecessarily to repeated doses of a substance already known to be safe at those levels. The dose in this trial escalates to a maximum of 25g/day which is the practical limit for consumption.

If any AEs are observed at 12g/day, the trial will regress back to 8g/day and run a cohort at that dose. If AEs are observed at 8g/day, it will de-escalate back to 4g/day. No AEs are expected at 8g/day, so this truncation of the escalation sequence has the potential of reducing the number of participants needed by between 9 and 18 without reducing the value of the data, (compared to a conventional 7-stage trial starting at 1g/day, which would require up to 42 participants).

To avoid confusion, the stages are labelled -3 to 4, skipping zero.

To avoid ambiguity, if the stopping rule fires at Stage 1 (12g/day), the de-escalation arm is automatically triggered rather than 8g/day being declared the MTI without testing.

To limit the number of capsules taken per day to 16 (and an absolute maximum of 20 in stage -2), the percentage of ABR in each capsule is increased at each stage.

The packaging is clearly marked which stage the intervention is to be used in and the number of capsules to be taken. The participant does not know how many stages there are, or what the stage number means.

6.5 Management of Investigational Trial Intervention Overdose

The maximum possible overdose is limited by the total amount of the intervention available to the participant. This amount is less than that required for a clinical overdose.

6.6 Preparation, Storage, Handling and Accountability of Investigational Trial Intervention

6.6.1 Preparation of Investigational Trial Intervention

The intervention is a UK food supplement prepared under food GMP conditions in the form of a Size 1 capsule containing the ABR. It is not a medical product for regulatory purposes.

The intervention is supplied by the sponsor.

It is recognised that food-supplement GMP standard is not equivalent to the Annex 13 (Manufacture of Investigational Medicinal Products) requirements, which we will refer to as medical GMP.

The production arrangements for ABRS if it were to be classified as an IMP are considerably stricter than general food GMP. The manufacturer's GMP does equate approximately to medical GMP, but are not certified to that standard at this time. The sponsor does not hold an MIA issued by the MHRA, as the intervention is not a medical product.

The QA measures in use include:

1. Deep Life Medical grows the ABR plant on 100 acre of farm it bought specifically for that purpose in Delta State, Nigeria.
2. The entire farming cycle is strictly controlled, with Standard Operating Practices (Work Instructions) in use throughout and covering every process.
3. The farms are managed by ten full time local staff and by two staff in the UK using remote monitoring and closely monitoring the results of the QA control measures outlined below. No pesticides are used and fertiliser is organic (chicken and pig manure, oil palm husk ash) plus Epsom salts (magnesium sulphate).
4. Every field of the farm has weekly soil analysis for NPK and moisture, weekly visual inspection using drones and the EOSDA satellite crop monitoring service with the high resolution premium.
5. All fields in production have automated irrigation.
6. Propagation is by using cuttings from a specific cultivar used by Deep Life Medical exclusively.
7. At the point harvest, the material is handled with appropriate PPE to avoid contamination, including gowns, hair nets, face masks, talc free gloves and overshoes. The raw root is washed in deionised water, the bark is removed and ground, then freeze dried within 6 hours. On removal from the freeze dryer the moisture content is measured, a sample taken for contaminant analysis and standardisation, then it is vacuum sealed. Following phyto-sanitary inspection, it is shipped to the UK for formulation into capsules using BP grade components, in a process with further strict controls.
8. Standardisation is performed on a per batch basis using GC-MS operated by a qualified biochemist in a government laboratory to measure key compounds in the batch.
9. In the UK, all material is kept frozen at -40C until ready for manufacture.
10. Formulation in the UK is under conditions that exceed food grade GMP and appear to be medical GMP but are not certified to Annex 13 (IMP GMP) as it is a food supplement.
11. Each batch has a certificate of analysis using GC-MS from a government laboratory, a phyto-sanitary certificate and a safety analysis to identify contaminants from a ILAP certified UK laboratory. DEHP is measured for each batch of ABR using GC-MS by an independent laboratory.
12. A silica gel desiccant is included in each tub of the intervention, marked clearly not to be eaten. Each tub is heat sealed, and fitted with a tamper evident cap. Labelling meets UK requirements for food supplements.
13. Every tub is laser marked with a serial number and expiry date.

6.6.2 Storage and Handling of Investigational Trial Intervention

The intervention is a foodstuff, and is issued by the sponsor to the investigator. The sponsor does not hold a MHRA MIA.

The intervention does not require freezing. It has a shelf life of at least three years based on measurement of key compounds using GC-MS on samples stored in warm conditions for 3 years.

Each tub is laser marked with a Use By date on the bottom of each tub.

The intervention can be stored at room temperature.

6.6.3 Accountability of Investigational Trial Intervention

The intervention will be shipped directly from the sponsor, upon the Principal Investigator advising the name and address to ship to.

The sponsor manufactures ABRS using the processes outlined. Each tub is serial numbered and the sponsor records which serial number is shipped where, when using a courier with confirmation of delivery. The sponsor provides that batch and serial number information to the Principal Investigator.

Unused product will be disposed of in general waste: it is a plant product without environmental risks.

6.7 Investigational Trial Intervention Assignment, Randomisation and Blinding

6.7.1 Participant Assignment to Investigational Trial Intervention

Participant identification codes are assigned on enrolment.

6.7.2 Randomisation

The manufacturer randomises the product, supplying two tubs to each participant at each stage: one tub is marked A and the other is B.

Assignment of A or B to the placebo or ABRS is performed using a PRBS. If the LSB output of the PRBS is zero, then A is assigned to the placebo and B to ABRS, if it is 1 then A is assigned to the ABRS and B to the placebo.

The PRBS execution is performed using a SPARK Ada program that has been verified to SIL3+ in a process certified to meet IEC EN 61508. The program uses a modified 32 bit PRBS generator, and offers the option for exact 50/50 distribution of sets if they are 2^n-2 in size: for each stage of this trial, 6 pairs will be made which is 2^3-2, so that option of a 50/50 random balance will be used so in each stage of dose, the 6 pairs (3+3) will have an equal number of A and B. In this trial, one cohort in each state will be in one centre, and the second cohort if needed will be in another centre on a different continent, with no communication between them.

A PRBS does not generate all zeros, the number of ones equals the number of zeros plus one, since the state containing only zeros cannot occur. That is, the probability of issuing 1s over 0 is 0.5 – (1/(2^64)-1). To make the probability exactly equal, the PRBS is modified to reject the all 1s output.

The PRBS is in a SPARK Ada program held by the sponsor, stored securely within the IT system to only partial access to manufacturing technicians who serialise the tubs of ABRS for trial purposes, and to the top level of IT staff.

The PRBS sequence once used, is encrypted, readable only by a SPARK Ada program that is used to determine the dose progression and to unblind on request from the DSMB. Investigators do not have access to the PRSB algorithm or the sequence.

The SPARK Ada program, called CT Manager (Clinical Trial Manager), is a commercial product. It maintains tamper proof logs of all interactions, meeting 21 Part 11 and European Annex 11. Log files are encrypted and can be viewed on the CT Manager tool or can be exported in human readable form, but not imported.

The AE assessment is indicated during an assessment window stated in Section 1.3. That assigned no AE if no AE is identified in an earlier assessment but can change to be an AE if a later assessment detects and AE.

The placebo is indistinguishable from the active product by appearance, taste, smell, and texture. A gel capsule is used. The only difference between ABRS and the placebo, is the placebo substitutes ABR for dried dandelion root. Kaolin is not the active component, so comprises the same proportion as for the ABRS in each dose. The salt content in the placebo matches the ABRS.

6.7.3 Measures to Maintain Blinding

The unblinding program does not reveal the blinding. The blinding is available only within the Sponsor's IT department. All actions taken by the program and all inputs are logged. Access is UID+password controlled, and logs the machine address and location used for access.

The packaging of the intervention is marked stating that it may contain a placebo, in an effort to reduce placebo effects.

6.7.4 Emergency Unblinding at the Site

The DSMB may request unblinding of a specific pair of tubs at any time from the sponsor who will instruct the IT department to provide the unblinding of those two tubs. The PI will be informed of the unblinding but not be unblinded other than disclosure by the DSMB in the event of a SAE.

6.8 Investigational Trial Intervention Adherence

The participants are monitored.

All tubs are serial numbered. The allocation of serial numbers to participant is recorded.

6.9 Description of Non-investigational Trial Intervention

Not applicable.

6.9.1 Background Trial Intervention

Not applicable.

6.9.2 Rescue Therapy

If the participant has a negative reaction to the intervention then the participant will be advised to drink water. The active components in the ABR are highly water soluble and pass out through urine.

If a SAE occurs, participants are instructed to treat it as a medical emergency and to obtain treatment without delay. All SAEs will be escalated by the PI and the DSMB will be advised promptly.

6.9.3 Other Non-investigational Trial Intervention

Not applicable.

6.10 Concomitant Therapy

6.10.1 Prohibited Concomitant Therapy

No restriction.

Participants taking any medication that could mask or confound TLE or AE assessment (for example, antiemetics, analgesics, or immunosuppressants), should be flagged to the PI for case-by-case.

6.10.2 Permitted Concomitant Therapy

No restrictions on concomitant therapy.

Concomitant medications taken by participants will be recorded and reviewed as per Section 6.10.1.

7 PARTICIPANT DISCONTINUATION OF TRIAL INTERVENTION AND DISCONTINUATION OR WITHDRAWAL FROM TRIAL

7.1 Discontinuation of Trial Intervention for Individual Participants

7.1.1 Permanent Discontinuation of Trial Intervention

The trial schema exposes each participant to only one dose of ABRS. The dose involves multiple capsules taken during the day.

Permanent discontinuation of the intervention will occur in the case of any of the following events:

1. the participant no longer meeting the enrolment criteria
2. the participant no longer wishing to be in the Trial (no reason need be given, but if the participant is willing to give the reason, then this shall be recorded).
3. the participant reporting a side effect from the intervention, which after review by the Principal Investigator, has a material safety risk.
4. the participant wishing to discontinue the intervention, but remain in the Trial.
5. A pre-participation medical test detects a condition making the participant ineligible for the Trial.

Following discontinuation, all available relevant data will be collected and reviewed by the Principal Investigator, including the reason for the discontinuation.

The number of participants who discontinue the Trial intervention and their reason will be reported in the Trial report.

7.1.2 Temporary Discontinuation of Trial Intervention

No situations identified in which temporary discontinuation is appropriate.

All safety related events shall be managed by review and permanent discontinuation.

7.1.3 Rechallenge

Rechallenge is not allowed**.**

7.2 Participant Discontinuation or Withdrawal from the Trial

The only reasons for a participant being considered withdrawn from the Trial is a participant's withdrawal of consent to continue to participate in the Trial, or if they no longer meet the eligibility criteria.

In these events, the participant will be asked whether that is a retrospective withdrawal, so no data can be used, or whether data collected up to the point of the withdrawal may be used.

All other participants, including those who discontinue Trial intervention, should remain in the Trial and continue to be followed to prevent missing data in important analyses. Refer to Section 10 Statistical Considerations for the data that must be collected for the Trial estimands.

7.3 Management of Loss to Follow-Up

In general, participants should be considered as lost to follow-up only if they cannot be reached despite multiple attempts to contact them.

Multiple, diverse methods shall be used to remain in contact with participants (e.g., telephone calls, texts, and emails to the participant). All contact shall be recorded on the sponsor's Electronic data

management system (eDMS comprising a secure portal into a SVN repository and Mantis+Jira for action tracking). The Jira configuration is validated to European GMP Annex 11.

If a participant that has enrolled but has not participated (i.e. not received any dose, whether placebo or intervention), then the participant shall be replaced by another who has enrolled and been screened (the medical examinations have been done, and the PI approves their participation after review of those results).

If the participant has enrolled and participated with one or two doses, and reports no symptomatic AEs, then the participant shall be replaced by another participant who has enrolled but not so far participated.

If the participant has enrolled and participated with one dose, and has no TLE but has circumstances that make the participant unavailable for the second dose as scheduled (i.e. after 7 days of washout), then the participant can either be discharged from the trial and be replaced by a new participant, who would take both dose A and B at the stage dose level, OR, if the original participant can participate in the second dose and medical examinations after a reasonable delay, then an extension to the washout period to accommodate that delay may be issued by the PI.

If the participant has enrolled and taken both doses, and has no TLEs, but is not available or unable or unwilling to have the second physical examination including blood and urine tests on time, i.e. the day after the second dose, then the participant shall be replaced by a new participant and the stage run at the same dose for that new participant.

8 TRIAL ASSESSMENTS AND PROCEDURES

8.1 Trial Assessments and Procedures Considerations

The active compounds in ABR are known to be soluble in aqueous solutions, and are absorbed rapidly through the oral route. This rapid delivery enables the Trial period to be short, for each participant.

8.2 Screening/Baseline Assessments and Procedures

The baseline screening is a physical examination, with a second screening following the dose, to detect any asymptomatic AEs. This medical assessment is carried out by an independent clinic contracted to the trial and paid for by the sponsor.

8.3 Efficacy Assessments and Procedures

This trial does not consider efficacy.

8.4 Safety Assessments and Procedures

The intervention is not a medicinal product, it is a food supplement on the general market.

8.4.1 Physical Examination

A pre-dose and post-dose medical history will be taken using a form developed for the trial. This includes a question on any allergies. The population from which participants are recruited is rural and from countries with a substantially lower prevalence of allergenic reactions than those in Western Europe or the USA.

A physical examination will be conducted for each participant, including vital signs measurement with ECG, standard haematology + blood panel (biochemistry), urine analysis. This will be performed at a clinic contracted by the trial.

Participants with SCD will additionally have ultrasonography of their liver and spleen. This scan may include other organs. For women, if ultrasonography is performed, it will include the uterus to confirm pregnancy, in addition to a urine or blood test for pregnancy.

Pre-dose in the context of the physical examination timing means before taking any dose from either Tub A or Tub B, and post-dose means after taking both Tub A and Tub B.

Where the pre-dose tests indicate a medical condition requiring treatment during the participation period, treatment will either be advised and organised through local doctors, or the participant will be discharged from the trial.

To avoid unnecessary replication of tests, and to ensure test results are available prior to participation, tests where samples were taken by accredited hospitals and laboratories up to 90 days before actual participation will be accepted.

The second physical examination would be conducted one day after taking the second dose.

For women of child bearing potential, the physical examinations will include a pregnancy test.

The PIL was amended to become revision A2 on 6th July 2026 (during the execution of Stage 2 of the trial), to include a clear statement on what use is made of the medical exam results, and where responsibilities lay with regard to any unexpected conditions that may be detected. All participants were provided with the additional text. The text enhances the participants' protection provisions and does not remove any right or expectation any participant would have reasonably had from the previous version of the form.

8.4.2 Vital Signs.

The physical examination includes vital signs.

8.4.3 Electrocardiograms

ECG is included within the physical examination described in Section 8.4.1.

8.4.4 Clinical Laboratory Assessments

The clinic carrying out the physical examination and the laboratory carrying out any analysis requested by the PI or DSMB shall be an accredited hospital or clinical laboratory, independent to the investigator and sponsor.

8.4.5 Pregnancy Testing

The inclusion and exclusion criteria exclude women of childbearing potential. Pregnant women are excluded from the Trial.

The physical examination includes a pregnancy test for participants who are women of childbearing potential to confirm the participant is not pregnant.

8.4.6 Suicidal Ideation and Behaviour Risk Monitoring

The intervention is not expected to have any association with suicidal ideation and or behaviour risk. Should any investigator becoming aware of a participant exhibiting such behaviour, that should be treated as a possible side effect and the intervention should be ceased immediately. The intervention is known to have a short washout period.

8.5 Pharmacokinetics

Not applicable.

Herbal supplements contain many compounds. GC-MS analysis rarely, if ever, adds up to 100% because of the presence of non-volatile solids, and other factors. Any health benefit is usually the result of

multiple compounds working synergistically. For these reasons, pharmacokinetic studies are not appropriate to herbal food supplements.

8.6 Biomarkers

8.6.1 Genetics, Genomics, Pharmacogenetics, and Pharmacogenomics

Not applicable as the intervention is a foodstuff.

8.6.2 Pharmacodynamic Biomarkers

Not applicable.

8.6.3 Other Biomarkers

None.

8.7 Immunogenicity Assessments

Not applicable.

8.8 Medical Resource Utilisation and Health Economics

Not applicable, the product is a food supplement.

9 Adverse Events, Serious Adverse Events, Product Complaints, Pregnancy and Postpartum Information, and Special Safety Situation

9.1 Definitions

9.1.1 Definitions of Adverse Events

An adverse event (AE) is any unfavourable or unintended sign, symptom, disease or abnormal laboratory finding that occurs during the period a participant is taking the intervention or in the month that follows.

The Common Terminology Criteria for Adverse Events Version 6[5] (CTCAE) shall be used. These are a set of criteria for standardised classification when recording adverse events of drugs and treatments (the definition includes "abnormal laboratory findings"), each with an associated severity scale in the range 1—5.

The classification of events uses the MedDRA at its granular (Lowest Level Terms: LLTs) level. For each term, specific conditions, findings and/or symptoms are stated for the different severity grades, which are organised as follows:

1. Mild
2. Moderate
3. Severe

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Common Terminology Criteria for Adverse Events (CTCAE) v6.0 (MedDRA 28.0) Published: July 22, 2025 U.S. Department of Health and Human Services. This section incorporates text from this source, which is in the public domain.

4. Life-threatening
5. Death if "related to the adverse event"

The guidelines used for grades 1 - 4 are:

Grade 1 - mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated.

Grade 2 - moderate; minimal, local or non-invasive intervention indicated; or limiting activities such as preparing meals, shopping for groceries or clothes, using the telephone, managing money etc. or (in paediatrics) mild/moderate impact on age-appropriate normal daily activity.

Grade 3 - severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; or limiting activities such as bathing, dressing and undressing, feeding self, using the toilet, taking medications – but not bedridden – or (in paediatrics) severe impact on age-appropriate normal daily activity.

Grade 4 - life-threatening consequences; or urgent intervention indicated.

Any mild symptom is treated as a TLE: this is a very low threshold, appropriate to the fact this is a trial of a food product. Food products are not normally expected to cause any AEs.

Symptoms prior to taking any dose will not be considered an AE or TLE, including the continuation of those symptoms during the period of participation.

Bruising from blood samples taken during screening shall not be considered as AEs or TLEs.

Asymptomatic Grade 1 laboratory findings expressed as negative differences between pre and post dose test results are classified as AEs but do not constitute TLEs unless accompanied by symptoms or judged clinically significant by the PI.

9.1.2 Definitions of Serious Adverse Events

The Trial will treat all Serious Adverse Events (SAEs) in the same manner as if the intervention were a medical product.

SAEs are defined under ICH E2A by specific criteria, namely a serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose that:

1. results in death,
2. is life-threatening[6],
3. requires inpatient hospitalisation or prolongation of existing hospitalisation,
4. results in persistent or significant disability/incapacity, or
5. is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

[6] The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

A SACE is by definition a SAE with at least a reasonable possibility of causal relation to the investigational product that is also unexpected relative to the reference safety information or product label. Thus, a SACE requires three criteria:

(1) **Seriousness**, meeting SAE criteria;

(2) **Suspected causality**, the investigator or sponsor judges a causal link is plausible;

(3) **Unexpectedness**, the event's nature or severity is not consistent with known information about the product.

By contrast, an SAE that is expected or not clearly product related is not reported as a SACE.

Sponsors must report any SACE to regulatory authorities (and ethics committees) on an expedited timeline of 7 days if the event is fatal/life-threatening, and 15 days for other SACEs.

9.1.3 Definitions of Product Complaints

A Product Complaint is any negative report from any participant.

9.1.4 Definitions of Medical Device Product Complaints

Not applicable.

9.2 Timing and Procedures for Collection and Reporting

This table describes the timing and procedures for collecting and reporting events.

Event Type	Situational Scope	Reportable Period Start	Reportable Period End	Timing for Reporting to Sponsor or Designee	Method for Reporting	Back-up Method for Reporting
Enrolment	Interview with participant	On enrolment	Singular event	Promptly	Word .doc file to be recorded on SVN in eDMS	None required
Recording Outcomes	Ditto	On completion of participation	On completion of intervention, and at start of any breaks in intervention	Promptly	Ditto	None required
Adverse Event	Report from participant or their medical team on any media	On enrolment	Singular event	Promptly	Through Jira, or backup media to Principal Investigator	Record on Jira on eDMS as primary, and through any other media to PI for record onto Jira as backup.
Severe Adverse Event	Ditto	On enrolment	Singular event	Promptly	Ditto	Ditto

Event Type	Situational Scope	Reportable Period Start	Reportable Period End	Timing for Reporting to Sponsor or Designee	Method for Reporting	Back-up Method for Reporting
Withdrawal	Report from participant or their medical team on any media	Any time during period of intervention	Singular event	Promptly	Ditto	Ditto
Analysis	By principal Investigator supported by Medical Statistics and IT team.	On receipt of first outcomes report	At end of Trial	Annual review, and then upon completion of Trial	Word .doc file to be recorded on SVN in eDMS	None required

9.2.1 Timing

Recorded in Table in Section 9.2

9.2.2 Collection Procedures

Provision of eDMS access to all investigators, and training on use of SVN, JIRA, MANTIS. All data is recorded on the eDMS.

Provision of multiple media reporting addresses, including email and phone to all participants and their medical teams to report any events. In recognition of phone use being limited in some territories, information over secure VoIP data services will be used additionally. Data from any source will be copied by screenshot to the Mantis system used by the sponsor to record events in a traceable manner. Data arriving on phones will be deleted after being archived onto Mantis.

Use of standard word processing packages producing .doc, .pdf & .xls format (e.g. Open Office, Adobe, MS Word), using standard forms for data collection.

9.2.2.1 Identification

Forms are used for enrolment and data collection, reviewed by the Principal Investigator, to collect the history and interventional data required.

A SPARK Ada program with UID and password access, logs all use on a central server, including input of AEs, MAC address of the user, date and time. This program implements the trial schema and advises on the escalation or de-escalation step required.

9.2.2.2 Severity

Severity is assigned grades using CTCAE criteria. AEs drive the TLEs which determine the MTI within the trial scheme.

As the intervention is a foodstuff, the bar for AEs to be treated as TLEs is very low, at a Grade 1 symptomatic AE that may have a possible causality from the intervention.

9.2.2.3 Causality

Causality is assigned by the trial schema.

9.2.2.4 Recording

Recording is by data entry onto documents loaded to Jira, Mantis and SVN in the sponsor's eDMS. and by the SPARK Ada program which implements the trial schema.

9.2.2.5 Follow-up

An investigator will follow up with interview of all participants at the start of each break, and at the conclusion of their participation.

9.2.3 Reporting

All data is collected Electronically and stored on the eDMS in standard formats, e.g. .doc files, .xls files, and as an XML file from the SPARK Ada program that implements the trial schema.

9.2.3.1 Regulatory Reporting Requirements

The Principal Investigator will report all significant events to the sponsor promptly, and provide regular updates on Trial progress.

The intervention is a food supplement, not an Investigational Medicinal Product. Accordingly, standard IMP regulatory reporting requirements do not apply to this trial.

However, in the interests of participant safety and transparency, the sponsor and Principal Investigator are committed to reporting any serious adverse event to the relevant authorities as a precautionary measure, as follows:

1. Any serious adverse event that may plausibly be associated with consumption of ABRS will be reported promptly to the UK Food Standards Agency and to the relevant food safety authority in the participant's country of residence, in accordance with food safety regulations.
2. As a precautionary measure, and consistent with the sponsor's commitment to maintaining a document trail suitable for future regulatory submissions, the MHRA will also be notified of any serious adverse event considered possibly related to the intervention.
3. Reporting timelines will mirror those applied to SUSARs under ICH E2A as a matter of adopting best practice: within 7 days for any fatal or life-threatening event, and within 15 days for any other serious event considered possibly related to the intervention.
4. All serious adverse events will be reported to the DSMB promptly for independent review.

No events meeting the strict definition of a SUSAR are anticipated, as that definition applies specifically to Investigational Medicinal Products. The term used in this trial for a serious adverse event considered possibly related to the intervention is Serious Adverse Consumption Event (SACE).

9.2.4 Adverse Events of Special Interest

Not Applicable.

9.2.5 Disease-Related Events or Outcomes Not Qualifying as AEs or SAEs

Not Applicable.

9.3 Pregnancy and Postpartum Information

9.3.1 Participants Who Become Pregnant During the Trial

There is limited opportunity for participants to become pregnant during the trial and for that pregnancy to be detected.

All participants who are women of child bearing potential have a pregnancy test during pre-dose physical medical examination. Women at higher risk will have an abdominal ultrasound scan of major organs:

while the trial will focus on the liver and spleen, the standard scan includes kidneys and uterus. Any pregnancy detected will result in the participant exiting the trial.

Participants are examined again 8 days after first dose participation. If the participant is pregnant in this second examination, they will be instructed to inform their obstetrician. At a minimum, depending on when the pregnancy is identified, a viability and fetal anomaly scan, followed by any additional monitoring as directed by the obstetrician, will be recommended at an appropriate time in the pregnancy.

9.3.2 Participants Whose Wife or Girlfriend Becomes Pregnant During the Trial

No action planned. This is appropriate as the intervention is a foodstuff with no compound classes present above the TDI published by the EFA.

9.4 Special Safety Situations

Special safety situations associated with the Trial intervention(s) that do not qualify as an AE or SAE, but require regulatory reporting. Examples include:

Situation	Response
Misuse or abuse	Not applicable: the total amount of the intervention is issued to each participant is less than the overdose amount. The intervention does not create dependencies.
Off-label use (if applicable)	Not applicable.
Medication error (prescription or dispensing error)	The intervention is issued by the sponsor in pre-packed tubs, which are sealed and temper evident.
Occupational exposure	Not applicable.
Use outside of what is foreseen in the protocol	Improbable.
Unintended exposure of embryo, fetus, or child via maternal exposure (pregnancy or breastfeeding) or via paternal exposure (semen)	Immediate cessation of the intervention for human participants who become pregnant. Depending on when the pregnancy is identified, a viability and fetal anomaly scan, followed by any additional monitoring as directed by the obstetrician, is recommended.
Lack of therapeutic efficacy; this is not applicable for studies that measure efficacy as a Trial endpoint	Efficacy is not considered in this trial.
Suspected transmission of an infectious agent; this is only applicable for injected or biologic medicinal products	The source material is washed in deionised water then freeze dried within 12 hours. Samples are tested for contamination by bacterial or fungal agents.
Product complaint, including falsified or counterfeit products	Unlikely given the small scale of the Trial and all interventional material is issued by the sponsor who produces it with total control of the entire process from farming the plant to formulation and packaging.

Situation	Response
Suspected drug-food or drug-drug interaction	Report as an AE.

10 STATISTICAL CONSIDERATIONS

10.1 General Considerations

The planned data analysis complies with ICH E9 and ICH E9(R1) guidelines.

The analysis is by an independent statistician with logged access to the sponsor's unblinding program: all other parties are blinded in this double blind trial.

10.2 Analysis Sets

All participants are included in the analysis.

The reference set is the set using the placebo.

10.3 Analyses of Demographics and Other Baseline Variables

No analysis of demographic variables is planned.

Age and ethnicity is reported on the data collection to support future analysis for association with these variables.

10.4 Analyses Associated with the Primary Objective(s)

10.4.1 Primary Objective

The analysis is whether a Tolerability-Limiting Event occurred that is associated with the intervention.

10.4.1.1 Statistical Analysis Method

Other than unblinding, the analysis involves running the trial schema.

The statistician has the schema coded as a spreadsheet script to indicate whether to escalate the dose, stop the escalation or to deescalate.

These are all basic processes specified within the trial schema.

10.4.1.2 Handling of Data in Relation to Primary Estimand(s)

The data for each primary estimand will be recorded in a spreadsheet, directly from examination of the report forms provided by the investigators. The spreadsheet shall be held on Jira and backed up to SVN.

10.4.1.3 Handling of Missing Data in Relation to Primary Estimand(s)

When data is missing, an investigator shall contact the participant to collect the missing information. If this is not successful, then the missing data will be considered on a case by case basis, and if significant, shall be handled as a withdrawal in accord with Section 7.3.

Withdrawals without a TLE having been reported, require the participant to be replaced and the stage doses repeated with the new participant. The trial may not progress to the next dose stage unless there is positive confirmation of no TLEs, which requires both doses to be taken by all three people in the cohort and the post dose medical examination (including ECG, blood and urine) being reviewed and compared with pre-participation data.

10.5 Analyses Associated with the Secondary Objective(s)

10.5.1 Secondary Objective

Solicit information on side effects by quantitative interview.

10.5.1.1 Statistical Analysis Method

Use of the trial schema.

10.5.1.2 Handling of Data in Relation to Secondary Estimand(s)

Data is handled in the same was as for primary estimands.

10.5.1.3 Handling of Missing Data in Relation to Secondary Estimand(s)

Data is handled in the same was as for primary estimands.

10.5.1.4 Sensitivity Analysis

Not applicable.

10.5.1.5 Supplementary Analysis

Not applicable.

10.6 Analyses Associated with the Exploratory Objective(s)

Not applicable other than basic statistical analysis.

10.7 Safety Analyses

All participants will be monitored by the Principal Investigator.

All persons connected with the trial are instructed to report all AEs to the Principal Investigator promptly, for review. The DSMB will be advised of all AEs.

If SAEs occur, PI will report to food safety agencies or the MHRA as required by current regulations.

No SAEs are expected as the ABRS has been in substantial use without SAEs being identified, and the population of this trial is small. If any SAEs occur, the Trial will be paused until they have been reviewed and if appropriate, additional safety characterisation has been carried out.

No AESIs (Adverse Events of Special Interest) have been identified.

10.8 Other Analyses

Not applicable.

10.9 Interim Analyses

An interim analysis will be conducted if the Trial is paused or suspended for any reason: See Section 4.3 Trial Stopping Rules.

An interim analysis may be performed at the request of an oversight body.

An interim analysis may be conducted in the event of any remarkable case reports.

All investigators and the sponsor can view the data during the progress of the Trial, other than personal information which only the Principal Investigator and the IT Manager for the sponsor's eDMS is able to access.

The analysis will be performed by an independent statistician.

10.10 Multiplicity Adjustments

The Trial will be considered to have met is primary objectives when sufficient data has been gathered to support a definitive conclusion.

No multiplicity adjustments are required for this Trial.

10.11 Sample Size Determination

The sample size is the smallest sample required to affirm or deny the hypotheses behind the primary estimands, for reasons of minimising risk and Trial overhead. The 3+3 cohort size is an established sample size for drug escalation trials, and is applied therefore to this trial of a food supplement.

11 TRIAL OVERSIGHT AND OTHER GENERAL CONSIDERATIONS

11.1 Regulatory and Ethical Considerations

This Trial will be conducted in accordance with the protocol and with the following:

1. Ethical principles that have their origin in the Declaration of Helsinki for medical research involving human subjects,
2. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines,
3. ICH Good Clinical Practice (GCP) Guidelines,
4. Applicable laws and regulations.

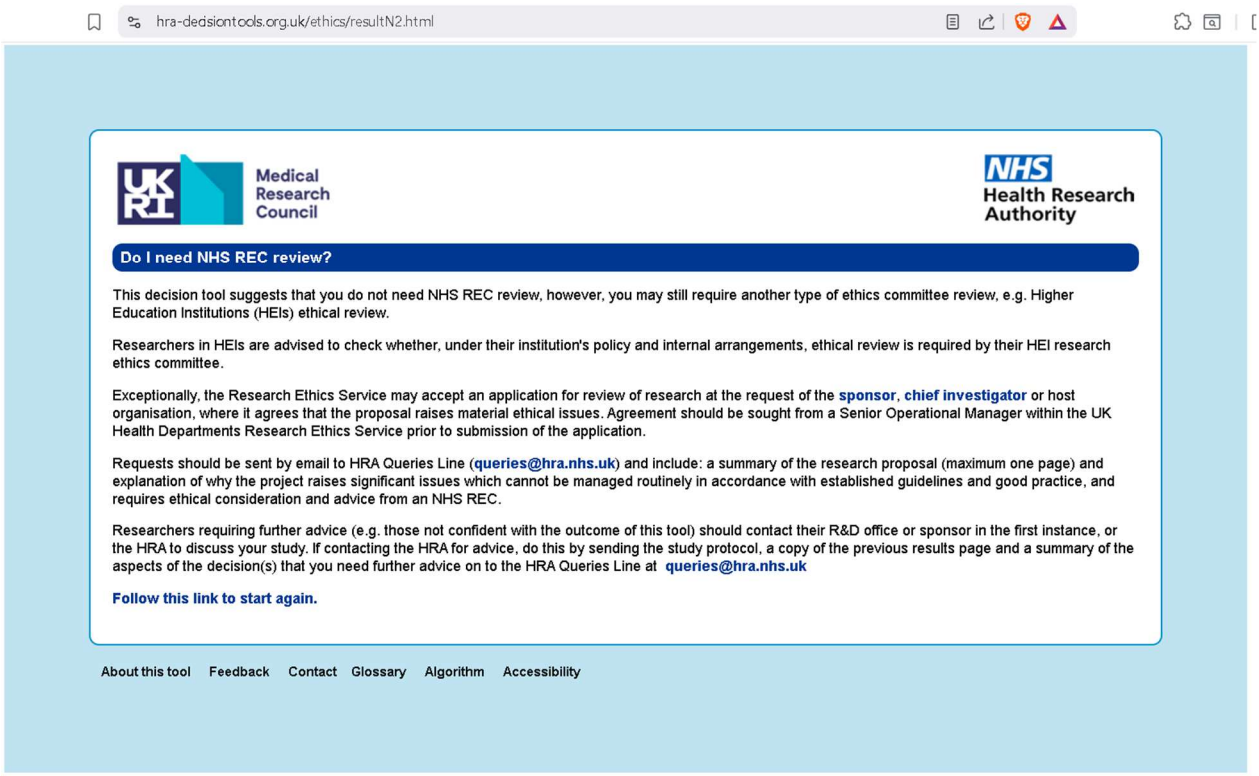
11.1.1 The Trial

ABRS is a food supplement on the general market in the UK, Europe with a ten year history of use in Europe. It has had substantial use for many generations in parts of South Eastern Nigeria. Food supplements do not normally have therapeutic benefit. Some food supplements are available both as a foodstuff for general use, and as prescription only for therapeutic use once those benefits have been proven scientifically through phased trials, e.g. Folic acid.

ABRS has no observed therapeutic benefit when taken by most users. It is observed that therapeutic benefits are claimed by two different user groups, with specific dosage regimens, but there is no scientific evidence of the reality of those benefits.

As a food supplement, the UK HRA Ethical Checklist on https://www.hra-decisiontools.org.uk was applied, generating certificates for Scotland, England and Wales, stating that no separate ethical approval body approval is required for this Trial. There is no certificate number generated by the tool, but a file with a link to the screen below (Exhibit 1). The REC review tool is maintained by the UK NHS. This trial uses no other NHS resources.

Exhibit 1: HRA Tool Output, Certificate Screenshot., accessed on 5th May 2026 The HRA certificates containing the link to this page are on the eDMS in SVN directory ABRS/INVESIGATIONS/ETHICAL_CASES covering Scotland, England and Wales.



As ABRS has not been proven to have therapeutic benefits, under MHRA Guidance Note 8 and the Human Medicines Regulations 2012, it would not be considered an Investigational Medicinal Product (IMP) for clinical trial purposes, requiring a full Clinical Trial Authorisation (CTA) via the combined review process (MHRA+REC).

This approach of not requiring a CTA is consistent with that of other trials of herbal products, as:

1. Edible herbal products are classified as foods, not medical products. This is well established in both UK and EU regulatory practice.
2. For almost every herb, or food, one can find many people claiming therapeutic benefits, whether it is cider vinegar, cold water, or any herb. Those anecdotal cases, regardless of their number, do not make the claim a scientific fact and do not form a basis for determining that a herb has a therapeutic benefit, and thence is an IMP. This is the standard position of the MHRA and EFSA on food supplement classification.
3. Many beauty products claim to contain compounds to have cell rejuvenation effects in vitro. This does not make them an IMP.
4. The compounds that make up herbal products are almost never known 100%: even with series MS-GS and HPLC, only 78% of the compounds in ABR are known. This would likely impede obtaining a CTA.
5. “Active” compounds identified in vitro, as the basis of health claims associated with herbal supplements, may have no effect in vivo.
6. The production of herbal products is required to meet food grade GMP, but are almost impossible to meet medical Annex 13 GMP, as they are a farmed product, manufactured in clean facilities with HACCPs in place, but not in cleanrooms.
7. The supply of herbal products is not through MIAs. An MIA is a legal requirement if a CTA is required. This is not practical for foodstuffs.

8. Foodstuffs, including herbal supplements, are consumed by people with all known medical conditions and diseases. The fact that a foodstuff is consumed by someone with a serious disease, does not make the foodstuff an IMP.

These factors are recognised so herbal remedies, herbal products and herbal supplements, are not normally registered for combined REC+MHRA approval, nor do they normally require a CTA, to carry out studies in the community. Despite this, this trial observes ICH Guidelines on good practice and establishes a traceable document trail such that if in a later trial a therapeutic benefit is found, then the document chain can support a CTA application at that stage.

This approach is consistent with published MHRA guidance and with the practice of other trials of herbal products in the UK.

The sponsors contacted Monica Wilde Msc (Herbal Medicine)UCLAN, ILADS, FLS, then, Director and Chief Research Herbalist in Napier Herbalists, the oldest herbalists in the UK, who confirmed this approach was correct and recommended it at the start of the investigations into ABRS. Dr Wilde's response is by email, recorded in the Master Dossier.

No NHS premises, NHS staff, or NHS data are involved in recruiting participants or conducting clinical assessments.

This protocol has been reviewed by the sponsor's ethical committee on 5th May 2026 and again on 28th June 2026. The committee does not include any staff currently employed by the NHS, nor NHS premises or data. Their report is available within their Master Dossier package. The ethical committee report considers a series of ethical principles and the series of conventions on clinical trials from the protocols listed in Section 11.1. The information above on the regulatory basis for this trial is from the ethical committee report. The report states that ISRCTN registration is a pre-enrolment condition for Phase 1 and Phase 2 trial it sponsors. Other than that requirement, the committee found no objection to this trial proceeding.

The trial was ISRCTN registered prior to the first participant being enrolled: ISRCTN51184184.

This update Rev A2 is made during the conduct of the trial to avoid errors from ambiguities detected during the execution of the trial. The resolutions and changes here do not affect any data already collected: there is no change to any dates or data in Stage 1 and the first half of Stage 2 (the point at which this A2 revision is rolled out), if this Revision A2 is applied instead of the Revision A1 that was used previously. The rollout of A2 is in a gap in activity between trial doses in Stage 2, but has occurred during a period when a participant was discharged from the trial prior to taking any dose upon discovery of undisclosed pre-existing medical conditions during screening. That former participant is being supported to have those conditions investigated in accord with the enhanced participant rights in the A2 revision of the PIL. The A2 revision of the PIL provides additional support to participants and does not take away any rights in the A1 revision of the PIL.

11.2 Trial Oversight

11.2.1 Investigator Responsibilities

In accord with ICH E6 Guideline on good clinical practice (GCP)[7], the Principal Investigator is a medical doctor familiar with the appropriate use of the investigational product as described in the protocol, the product information and the information sources provided by the sponsor. The Principal Investigator has had specialist training as a clinical investigator.

Those guidelines state:

[7] ICH E6 Guideline on good clinical practice (GCP) International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use 23 Jan 2025, https://ichgcp.net/2-investigator-ich-e6-r3

1. The investigator may delegate Trial-specific activities to other persons or parties. The investigator may be supported by the sponsor in the identification of a suitable service provider(s); however, the investigator retains the final decision on whether the service provider intended to support the investigator is appropriate based on information provided by the sponsor.
2. The investigator retains the ultimate responsibility and maintains appropriate oversight of the persons or parties undertaking the activities delegated to ensure the rights, safety and well-being of the Trial participants and the reliability of data. The level of investigator oversight of the delegated activities should depend on the nature of the delegated activities and is proportionate to the importance of the data being collected and the risks to Trial participant safety and data reliability.
3. The investigator should ensure that persons or parties to whom the investigator has delegated Trial-related activities are appropriately qualified and are adequately informed about relevant aspects of the protocol, the investigational product(s) and their assigned Trial activities (including activities conducted by staff provided by other parties in accordance with local regulatory requirements). Trial-related training to persons assisting in the Trial should correspond to what is necessary to enable them to fulfil their delegated Trial activities that go beyond their usual training and experience.
4. The investigator should ensure a record is maintained of the persons and parties to whom the investigator has delegated Trial-related activities. Documentation of delegation should be proportionate to the significance of the Trial-related activities. In situations where the activities are performed as part of clinical practice, delegation documentation may not be required.
5. Agreements made by the investigator/institution with service providers for Trial-related activities should be documented.
6. The investigator/institution should permit monitoring and auditing by the sponsor, inspection by the appropriate regulatory authority(ies) and, in accordance with applicable regulatory requirements, review by IRB/IEC(s).

11.2.2 Sponsor Responsibilities

The sponsor supports independent clinical trials of its products, providing the PI with:

1. Trial schema design and review,
2. providing sufficient quantity of the intervention for the purposes of the Trial produced in accord with UK legal requirements for food supplements, marked with trial labelling, randomisation and with ABR dosing matching the specification from the trial schema,
3. providing the eDMS system, including SVN, Jira and Mantis access for the investigators,
4. providing access to their Master Dossier for investigators, on a NDA basis,
5. providing access to their preclinical report and confidential Master Dossier,
6. funding receipted costs, including the DSMB fees,
7. independent statistical analysis of the results where required, and use of a SPARK Ada program which implements the trial schema without disclosing the blinding, based on the PI indicating when AEs occur for given pairs of ABRS serial numbers.
8. providing the DSMB with logged access to its unblinding software, which informs whether any specific tub serial number is ABRS or placebo and confirms the dosage in tub,
9. funding publication of the Trial results,

10. QHS&E management of the Trial in accord with its ISO 9001:2015 certified procedures. The sponsor has ISO 13485:2016 certified procedures for its medical devices, but not for medicines: it produces ABRS as a food supplement, not as an Interventional Medical Product.
11. advising the investigators promptly of any AE or other event that may give rise to safety questions.
12. The sponsor will cover the cost of first-round additional diagnostic tests and an initial consultation with a local physician where pre-participation screening identifies an unexpected finding requiring further investigation. For findings assessed as potentially critical, the sponsor will cover further diagnostic tests until treatment options are identified. These costs are distinct from treatment costs, which remain the participant's responsibility except where illness is plausibly attributable to trial participation.

11.3 Informed Consent Process

The Trial excludes participants with a disability affecting assent, capacity, or who require a legally acceptable representative, and adolescents who may reach age of majority during the Trial.

All participants must be literate. There is no assessment for literacy, other than the PIL will be discussed with each participant before enrolment, and investigators will not enrol someone who appears to have problems in understanding the information presented in the PIL.

The PIL and ICF is provided in the language in which the participant is fluent in writing. This is normally English. If a participant is not fluent in English, then the PIL and ICF will be translated into their language and all explanations, discussion and reports will be in that language.

The PIL is provided to the prospective participant and an investigator walks through the PIL, prior to the prospective participant being asked for consent. After the prospective participant has received that information and any questions answered the enrolment confirms the prospective participants validity to join the Trial, the participant is asked to sign the informed consent form used by the Trial.

Enrolment will not occur during an emergency in which the participant or their legally acceptable representative is not able or available to give consent.

11.3.1 Informed Consent for Re-screening

If participants are re-screened following the process described in Section 5.6 Screen Failure and Re screening, the participant may need to complete a new ICF depending on the circumstances: that need will be determined by the Principal Investigator on a case by case basis.

11.3.2 Informed Consent for Use of Remaining Samples in Exploratory Research

Not Applicable.

11.4 Committees

The DSMB board is made up of a GMC registered doctor (who is not the PI).

The sponsor audits the conduct of the trial at all key events. This audit is by a senior.

A Nigerian user of ABRS is available to all involved in the trial for cultural liaison and translation.

These committees are appropriate as the item being tested is a food with a long history of substantial use.

The sponsor employs persons qualified in mathematics and statistics and those persons are available to the DSMB at any time but as they are employed by the sponsor, are not formally members of the DSMB.

11.5 Insurance and Indemnity

Participant insurance and indemnity is addressed in the PIL, which meets the applicable regulatory requirements. Insurance is held by Deep Life Medical Ltd. Deep Life Medical Lda's role does not extend to participant-facing obligations. The PI holds a separate insurance and professional indemnity policy.

All policies referred to, exclude the USA.

11.6 Risk-Based Quality Management

The sponsor is providing the quality management for the Trial.

The sponsor is ISO 9001:2015 and ISO 13485:2016 certified, and its systems meet IEC 61508:2010, considered the "Gold Standard" in functional safety and from which PPE and other sector specific standards are derived. In the absence of specific standards, those processes as they apply to risk, compliance, documentation, traceability and review, are applied to its nutraceuticals and food supplement activities.

A HACCP is in place for the sponsor's nutraceuticals and food supplements.

The sponsor has risk based quality management processes that include clinical trials: these are for medical devices, but are applied to all products and projects that the sponsor funds or performs.

11.7 Data Governance

The sponsor's eDMS will be used to manage all trial data, documents and information. This is on a secure server and comprises SVN, Jira and Mantis applications, providing full traceability for all data submission and changes.

The sponsor's eDMS has been certified by a UKAS accredited agency to meet the strict standard of IEC 61508:2010 for use at SIL 3+, with end to end scope covering all safety projects, not just electronic and software projects. The Jira configuration within this is configured for 21 CFR Part 11 compliance, and validated to EU GMP Annex 11.

Data collection is primarily by quantitative interview using a structured questionnaire. The data is stored on SVN and compiled as spreadsheets during analysis.

11.8 Data Protection

A Data Protection Impact Assessment (DPIA) has been conducted and a report is included in the Master Dossier.

UK Data Protection regulations apply. For EU participants (including those enrolled through the Portuguese co-sponsor), GDPR (EU 2016/679) applies.

All data is collected and held in the UK. All data collectors and persons with access to the data have had GDPR training including training specific to the handling of personal medical data.

The consent form gives specific consent for the personal data collected by the trial to be stored by the PI and by the sponsor. This meets UK GDR Article 9 requirement that the data subject has given explicit consent to the processing of that personal data for one or more specified purposes.

The processing meets a general lawful basis under Article 6 and one of the specific conditions outlined in Article 9(2), and DPA 2018, specifically Schedule 1, Part 1, Condition 4 a,b,c (Research).

A primary data risk is the use of WhatsApp for communication. WhatsApp is the only means of communication available to most of the expected participants. WhatsApp is end to end encrypted. The risk is mitigated by a process that following communication on WhatsApp, the chat is printed out and

deleted from the receiving devices. Participants are informed of this deletion and archive. The deletion is automatic: it uses a WhatsApp chat deletion timer.

The identity of the participants is held on a paper file in a safe in a secure room separately to the Trial data. Medical exam reports and lab results that identify the participants is held in the same file. There are two copies of a USB drive on that otherwise paper file, to record items that cannot be printed out, or which may be needed in electronic form later such as video recordings and scans. That data is accessible only by the Principal Investigator, Sponsor's Head of Compliance, and persons the PI authorises.

The Trial complies with UK regulations on personal data protection.

In the case of a data security breach the participants will be informed promptly.

11.9 Source Records

All source records will be maintained for 15 years in accord with the sponsor's QHS&E system.

Traceability is provided by the sponsor eDMS.

A source record is any of the production batch data, enrolment forms, data collection forms, and documents created during the course of the Trial including the analysis, result reporting and papers.

11.10 Protocol Deviations

Deviations from protocol will be detected by the Principal Investigator during normal monitoring or review activity. The sponsor will also review the conduct of the trial before approving publication. The sponsor does not have the authority to prevent publication, only the authority to refuse to indicate its approval to publication.

Deviations will be reported to the Principal Investigator for consideration.

11.11 Early Site Closure

Only the Principal Investigator has the authority to close a site early.

Early closure may occur if the Trial protocol is not being followed on that site, and no adequate rectification has been determined.

All participants on that site, and the sponsor, will be informed promptly. Follow up arrangements will be determined by the Principal Investigator on a case by case basis.

11.12 Data Dissemination

The clinical Trial will be registered in public databases, including reporting of results.

Results will be published after analysis. Anonymised raw data will be available for third party audit.

12 APPENDIX: SUPPORTING DETAILS

12.1 Clinical Laboratory Tests

Blood tests at baseline and post-dose will be obtained. This will be from a clinic contracted to this study.

12.2 Country/Region-Specific Differences

None.

12.3 Prior Protocol Amendment(s)

The Protocol Amendment Summary of Changes for the current amendment is located directly before the Table of Contents.

Prior amendment(s) to this protocol are listed in the Revision History on Page 1.

An Overview of Changes from each prior protocol amendment is provided in the document history on Page 1.

13 APPENDIX: GLOSSARY OF TERMS AND ABBREVIATIONS

Abbr or phrase	Meaning
ABR	African Bitter Root
ABRS	African Bitter Root supplement, combining normalised ABR (4.6%) sodium chloride (0.4%), and kaolin (remainder)
AE	Adverse Event
AR	Adverse Reactions (an AE with possible causality from the ABRS)
FSM	Finite State Machine
GC-MS	Gas chromatography–mass spectrometry
HPLC	High Pressure Liquid Chromatography
IMP	An interventional medical product
MTI	Maximum Tolerable Intake
NIMP	Non-Investigational Medicinal Product
PIL	Participant Information Leaflet
SAE	Serious Adverse Event
QA	Quality Assurance
QHS&E	Quality, Health, Safety and Environment management system.
SACE	Serious Adverse Consumption Event
SUSAR	Suspected Unexpected Serious Adverse Reaction, a term used for medical products instead of SACE.
TDI	Tolerable Daily Intake
TLE	Tolerance-Limiting Event
Traditional Medical Care	Medical care using herbal treatments instead of modern Western medicines
Traditional Medicine	A substance with a long history of traditional use, which may or may not meet the definition of an IMP.
Western medicine	A therapy or treatment approved by a national body in Europe , Japan, Australia or North America that is accredited to the ICH.

14 APPENDIX: REFERENCES

References are made by footnote.

The following documents accompany this protocol:

1. Participant Information Leaflet.
2. Participant Consent Form.
3. Deep Life Medical's ethical review of this trial protocol.
4. CONSORT checklist.