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	9th May 2026 Date
_____/KB/_____ Quality Officer of Sponsor	9th May 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.

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:	A0
Version Date:	9th May 2026
Amendment Identifier:	A0
Amendment Scope:	Global
Sponsor's Investigational Product Code(s):	ABRS-AR-250mg-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.
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)	ISRCTN registration is a pre-enrolment condition. ISRCTN number is to be assigned prior to enrolment.
Sponsor Approval:	9th May 2026.

Sponsor Signatory: Alex Deas, PhD 9th May 2026 Dr. Alex Deas Signer ID: 3PAJ9DOH2O... ✓

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 members will be fully independent of the sponsor and the PI.

The sponsor 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, use of its QA system including its eDMR for document storage, panel for review of documents and supply of ABRS.

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 has been not been amended previously. Details of amendments will be presented in Section 12.3 Prior Protocol Amendment(s).

This document includes changes from pre-submission review comments.

Current Amendment

The table below describes the current amendment.

Approximate Enrolled at Time of Sponsor Approval:	0%	
Reason(s) for Amendment:	New document	Secondary: Not Applicable
Amendment Summary:	Not Applicable	
Is this amendment likely to have a substantial impact on the safety or rights of the participants?	No	
Is this amendment likely to have a substantial impact on the reliability and robustness of the data generated in the clinical Trial?	No	

Overview of Changes in the Current Amendment

Description of Change	Brief Rationale for Change	Section # and Name
Adoption of updated ICH template	QA Compliance.	All

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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-250mg	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 toxicity events are reported during the placebo period.

1.1.2.3 Blinded Roles:

The following roles indicated will not be made aware of the treatment group assignment during the trial: Principal Investigator, All Investigators, All Participants and the DSMB.

The DSMB can request emergency unblinding in the event of a SAE.

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 (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 7 day washout is used to prevent misallocation of residual AEs to placebo when they arise from ABRS.Committees

Refer to Section 11.1, 11.2

1.2 Trial Schema

The trial follows the 3+3 Dose-Escalation procedure below.

1. **Trial Setup**
    a. Start trial and enrol an initial cohort of 3 participants. A participant participates at only one dose level.
    b. 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.
    c. Administer doses according to protocol. Participant takes all of pack A, waits the washout period (initially 7 days), then takes all of pack B.
    d. Assess safety and record dose-limiting toxicities (DLTs) 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 DLT events are reported to the DSMB promptly.
    e. The DLT assessment is performed by a SPARK Ada computer program which has the 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 DLT occurred (if any). It determines whether the reported toxicity event 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 to screen reported DLTs from placebo use.
        i. If the reported DLT is for a participant on the placebo who has not had ABRS then the program instructs the investigator to substitute that participant and rerun that dosage with the new participant.
        ii. If the reported DLT is for a participant who has used ABRS that day, it is treated as a DLT.

iii. If the reported DLT is for a participant who used the placebo that day, 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.

iv. If a DLT occurs during the ABRS period, but the participant previously took the placebo and had a DLT during that period too, then the whole cohort of 3 should be re-run.

2. **Apply 3+3 decision at current dose**
    a. If 0 DLTs in the first 3 participants, escalate to the next higher dose with a new cohort of 3.
    b. If 1 DLT in the first 3 participants, expand the cohort to 6 participants at the same dose.
    c. If 2 or more DLTs in the first 3 participants, stop escalation and designate the previous lower dose as the MTD candidate.
3. **Expanded cohort review**
    a. Continue treatment and monitor safety for all 6 participants.
    b. If total DLTs are 1 or fewer out of 6, escalate to the next dose.
    c. If total DLTs are 2 or more out of 6, stop escalation and designate the previous lower dose as the MTD candidate.
4. **Escalation loop and stopping**
    a. Repeat the dose-escalation steps for subsequent dose levels until a stopping rule is met or the highest planned dose is tested.
    b. The dose is a modified Fibonacci sequence starting at 1g/day and a maximum of 25g/day, with the first dose entry point in the series is at 12g/day. The series allows for de-escalation of dose downwards from 12g if AEs occur.
5. **Trial completion decision**
    a. If the highest planned dose is completed without unacceptable toxicity, select the highest tested dose as the MTD for further study.
    b. If the highest planned dose or stopping rule shows unacceptable toxicity, select the previous safe dose as the MTD for further study.
6. **Close trial**

    End the trial and document the selected dose and safety outcomes.

The participation scheme is for each participant.

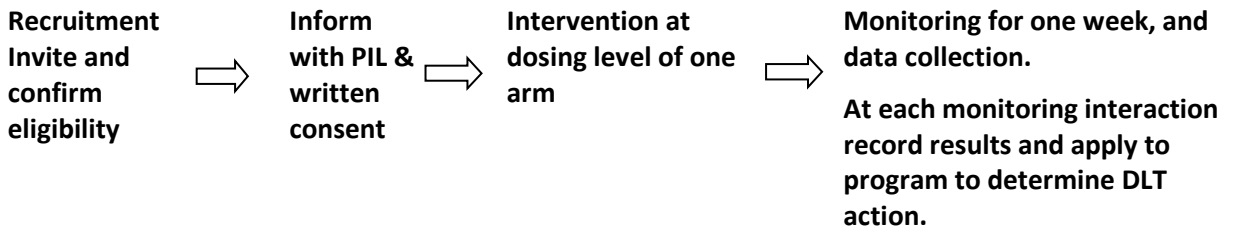

Figure 2: Participation Scheme

The dosage scheme 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 100 of the standard 250mg capsules per day. That means, the initial dose is 12g/day, maximum dose is 25g/day, theoretical minimum dose with full de-escalation is 1g/day.

A DLT is a Grade 1 symptomatic AE, or higher AE using CTCAE criteria. This very low threshold is appropriate to a trial of a food product. Food products are not normally expected to cause any AEs, whether taken for general health as a food supplementation or as a foodstuff.

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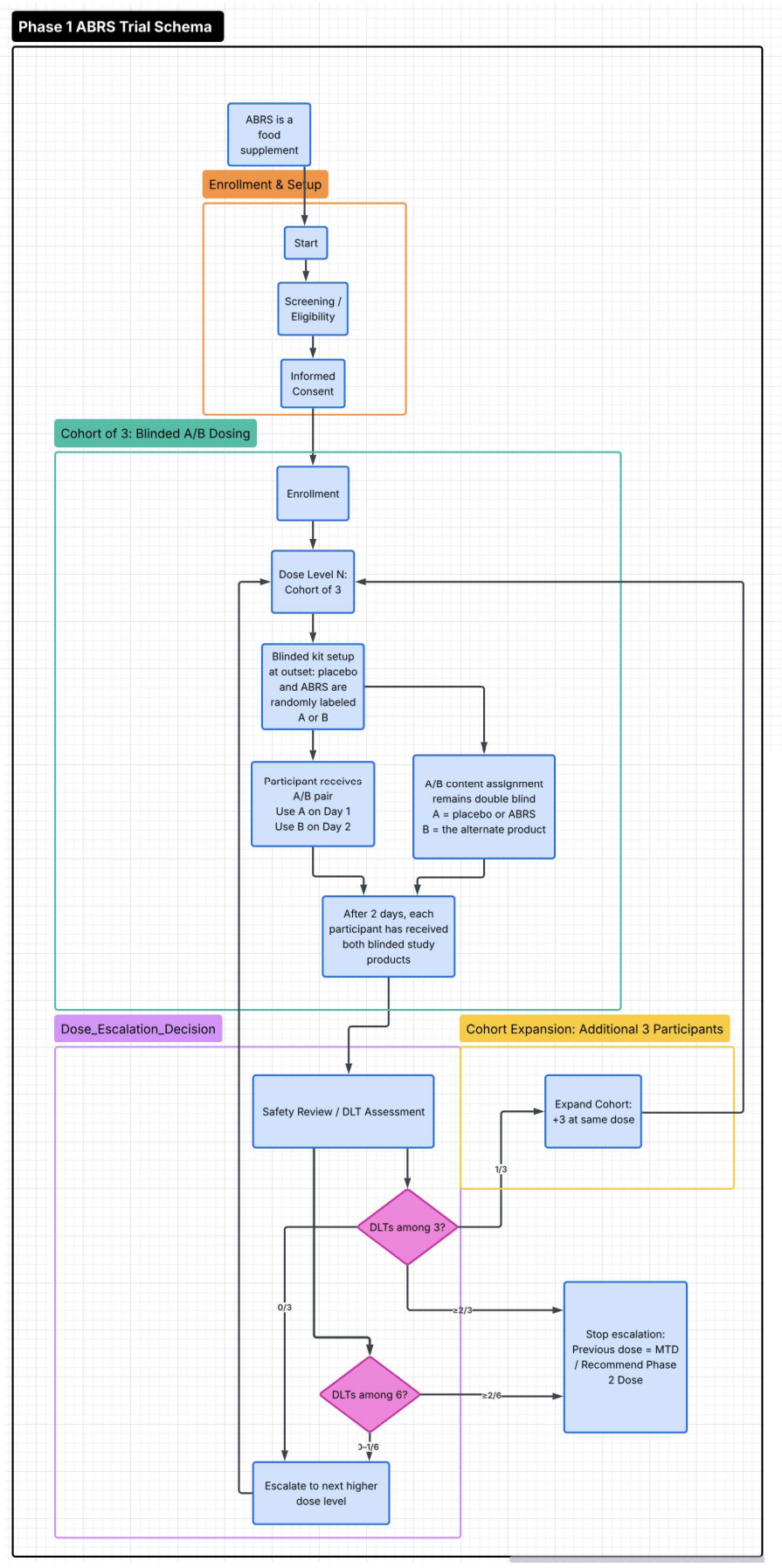

Figure 1: Trial Scheme to determine Maximum Tolerable Dose (MTD).

The algorithm used for the DLT 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

1.3.1 Activity Timeline

Activity	Screening / Enrolment	Pre-dose Examination (Day 1)	Tub A Dose (Day 1)	30 min post Tub A	1 hour post Tub A	Day 2 (1 day post Tub A)	Day 7 (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												

Activity	Screening / Enrolment	Pre-dose Examination (Day 1)	Tub A Dose (Day 1)	30 min post Tub A	1 hour post Tub A	Day 2 (1 day post Tub A)	Day 7 (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)
Physical examination (contracted clinic)		✓									✓	
Vital signs (BP, HR, temperature, respiratory rate)		✓									✓	
ECG		✓									✓	
Haematology + biochemistry blood panel		✓									✓	
INTERVENTION												
Issue Tub A and Tub B to participant		✓										
Administer Tub A (self-dose, empty stomach, water) observed by investigator.			✓									
Administer Tub B (self-dose, empty stomach, water) observed by investigator.								✓				

Activity	Screening / Enrolment	Pre-dose Examination (Day 1)	Tub A Dose (Day 1)	30 min post Tub A	1 hour post Tub A	Day 2 (1 day post Tub A)	Day 7 (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)
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						✓						
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	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Activity	Screening / Enrolment	Pre-dose Examination (Day 1)	Tub A Dose (Day 1)	30 min post Tub A	1 hour post Tub A	Day 2 (1 day post Tub A)	Day 7 (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)
(eDMS)												
Apply DLT assessment via SPARK Ada program						✓	✓				✓	✓
SAFETY AND ESCALATION												
Report all DLTs 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 DLTs 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, on Day 1 prior to administration of Tub A.

Post-dose examination: Conducted at the same contracted clinic on Day 9, one day after administration of Tub B, after the participant has received both blinded study products.

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. All responses are recorded on the eDMS.

DLT assessment timing: The SPARK Ada program applies the DLT assessment algorithm at the end of each assessment window: Day 2 and Day 7 for Tub A, and Day 9 and Day 15 for Tub B. The assessment window runs from the first dose to seven days after the second dose.

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.

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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.
Intervention	Provide two tubs of 250mg capsules of ABRS to participant, marked A and B. 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.
Monitoring	Obtain feedback for each intervention dose, prior to intervention, 30 minutes after starting each intervention, an hour, 1 day and one week after. Additionally, two 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.

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.

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

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 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 :

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

[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.

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.)

- **TDI/NOAEL**: Not applicable (natural metabolites / food components).
- **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.)

- **TDI**: None established (common in fruits/vegetables).
- **NOAEL** (ferulic acid example): ≥2,000 mg/kg/day.
- **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)

- **TDI**: None established (Maillard reaction product in cooked foods).
- **NOAEL**: 80–100 mg/kg/day (5,600–7,000 mg/day for 70 kg adult).
- **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)

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

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

- **TDI/NOAEL**: No specific values; all occur at trace levels or are common plant volatiles.
- **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.

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 (MTD) 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 DLT.
Population-level Summary	The Trial is measured by counting DLTs.
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 is 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.

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:

1. CARE Guidelines for Case Reports, 2013[3].
2. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups.
3. STROBE: Observational Studies[4].

4.2.1 Rationale for Estimand(s)

The MTD 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.

[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

4.2.2 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.

4.2.3 Rationale for Control Type

The trial involves ingesting large numbers of tablets: 16 capsules. This may cause false DLTs, 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 DLTs 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.

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 will be registered with ISRCTN prior to enrolment starting.

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

The Trial shall finish when the MTD 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.

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 in English, 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,
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,
6. The PI's professional liability insurance excludes the USA so no participants may be enrolled who are in the USA or who hold passports from the USA.

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, or bilateral tubal ligation, 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.

Reference to male and female are applied on the basis of their 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

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 OO.	5% 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, 250mg capsules	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 OO sized capsules.

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 dose and regimen is stated in Section 4.1

The intervention is delivered in the form of 250mg capsules, OO sized. 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 the lowest dose observed to be in routine use.

1g/day is two of the standard capsules, two times 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 250mg/capsule product would be 100 capsules. This is impractical for consumption, so the percentage of ABR in ABRS 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
-3	1	1	-	4.6	4
-2	2	4	4.00	4.6	16
-1	3	8	2.00	9.2	16
1	8	12	1.5	13.8	16
2	13	16	1.33	18.35	16
3	21	20	1.25	22.94	16
4	34	25	1.25	28.68	16

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 the lowest standard dose recommended by the manufacturer, based on its observations of traditional use. Common dose levels in indigenous use are from 4g to 8g/day. No user has been observed to have any adverse effects attributed to ABRS. The dose escalates to a maximum of 25g/day which is the practical limit for consumption. The dose of 25g/day is known to have been taken by one traditional user without adverse effects.

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 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.

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 MTD without testing.

To limit the number of capsules taken per day to 16, 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.

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 an OO sized 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 placebo or ABRS uses a modified 64 bit PRBS generator. 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.

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 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 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 AE assessment (for example, antiemetics, analgesics, or immunosuppressants), should be flagged to the PI for case-by-case review.

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.

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).

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

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. The 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.

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.

[5]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.

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
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 DLT: 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.

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 SUSAR 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 (e.g. Investigator's Brochure or product label. Thus, a SUSAR 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 IMP.

By contrast, an SAE that is expected or not clearly drug-related is not reported as a SUSAR.

Sponsors must report any SUSAR 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 SUSARs. The EU Clinical Trials Information System (CTIS) would be used. The MHRA will be asked to clarify whether MHRA safety reporting obligations apply to a non-IMP food supplement trial.

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.

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
Severe Adverse Event	Ditto	On enrolment	Singular event	Promptly	Ditto	Ditto
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 DLTs which determine the MTD within the trial scheme.

As the intervention is a foodstuff, the bar for AEs to be treated as DLTs is very low, at a Grade 1 symptomatic AE.

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.

Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting timelines: SUSARs must be reported to the MHRA within 7 days (fatal/life-threatening) or 15 days (other), using the same process as if the product were a medical product. The relevant food authorities will also be advised.

Reports will be shared between the investigators.

All AE and SAEs will be reported to the Principal Investigator directly, for urgent review.

There are no additional regulatory reporting requirements for this Trial.

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

All participants who become pregnant during the Trial will be instructed to cease use of the intervention immediately and 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, is recommended.

9.3.2 Participants Whose Partners Become 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

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.
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 toxicity 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.

Withdrawals are imputed to mean that a DLT may have occurred, requiring the cohort to be repeated.

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:

- Ethical principles that have their origin in the Declaration of Helsinki for medical research involving human subjects,

- 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,
- ICH Good Clinical Practice (GCP) Guidelines,
- Applicable laws and regulations.

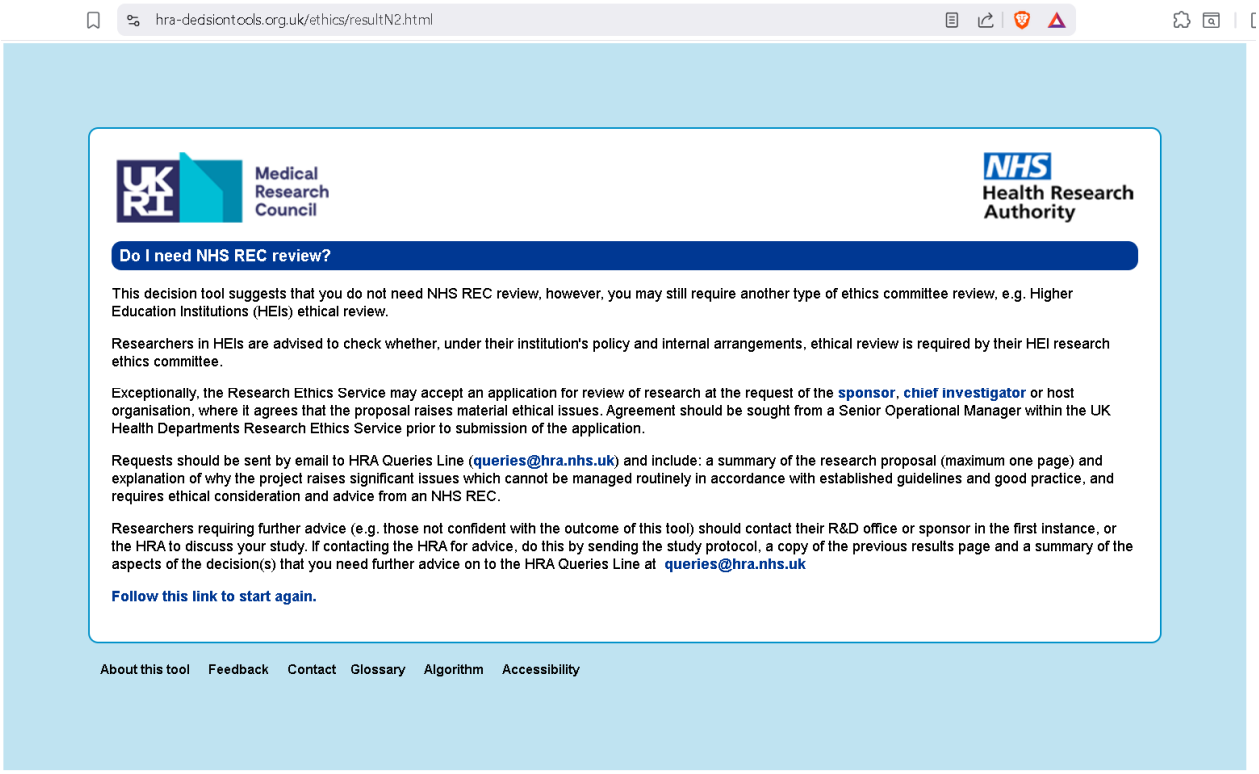
11.1.1 The Trial

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. 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 ISRCTN trial registration will be completed before the first participant is enrolled, and the ISRCTN number inserted into the protocol header at that point

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:

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,

[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

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.

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.

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

A single independent GMC registered doctor provides the DSMB. This is 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.

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.

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

The identity of the participants is held on a secure server separately to the Trial data. That server is accessible only by the Principal Investigator and the IT Manger.

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.

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

This protocol has been developed from earlier drafts and proposals, with incorporation of reviewers comments of draft documents. It is presented as a new protocol.

Overview of Changes in Amendment

Refer to Revision 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 (5%) sodium chloride (0.4%), and kaolin (remainder)
AE	Adverse Event
DLT	dose-limiting toxicities
GC-MS	Gas chromatography–mass spectrometry
HPLC	High Pressure Liquid Chromatography
IMP	An interventional medical product
MTD	Maximum tolerated dose
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.

SUSAR	Suspected Unexpected Serious Adverse Reaction
TDI	Tolerable Daily Intake
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.