APPENDIX 3 to the PROTECT Platform Master Protocol

This appendix must be read with the accompanying PROTECT Platform master protocol IRAS 353122. This appendix describes only the additional details relevant to the conduct of this randomised comparison within the context of the overarching master protocol.

Full Title	Diversity in perioperative research
Short Title	PROTECT-DIVERSITY
PROTECT-DIVERSITY IRAS Number	350756
PROTECT IRAS Number	353122
REC Reference	24/LO/0887

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Participating sites	For a list of participating sites please refer to the IRAS application

Comparison Contributors

The Sponsor and funders have not played, nor will play a role in the study design, conduct, data analysis and interpretation, manuscript writing, and/or dissemination of results.

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1. Contents

2. Glossary of comparison specific terms and abbreviations

CMG	Comparison Management Group
GCP	Good Clinical Practice
PI	Principal Investigator

3. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

PROTECT Platform Chief Investigator: Dr Tom Abbott

Signature: Tom Abbott Digitally signed by Tom Abbott Date: 2025.02.06 13:04:16 Z

Date:

PROTECT-DIVERSITY Lead Investigator: Dr Tom Abbott

Signature: Tom Abbott Digitally signed by Tom Abbott Date: 2025.02.06 13:04:37 Z

Date:

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for the statistical work in this protocol is accurate and take responsibility for statistical analysis and oversight in this study.

Statistician's name: Kamran Khan

Signature: Kamran Khan Digitally signed by Kamran Khan Date: 2025.02.06 14:03:54 Z **Date:**

Principal Investigator Agreement

The clinical study as detailed within this research protocol **(version xx.xx, dated xx.xx.xxxx)**, or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the UK Policy Framework for Health and Social Care Research , the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator:

NHS site:

Signature: **Date:**

4. Summary and synopsis

Full title	Diversity in perioperative research
Short title	PROTECT-DIVERSITY
Study design	Multi-centre individual patient randomised trial
MHRA risk level	N/A (non-CTIMP comparison)
Phase of trial	IV
Study setting	Surgical services of NHS hospitals
Medical condition or disease under investigation	Adult patients undergoing elective surgery
Objectives	• Compare the impact of using multi-lingual consent forms with consent forms in English on the ethnic diversity of patients included in the study • Compare the accuracy and completeness of protected characteristics data collection using different methods
Inclusion and exclusion criteria	*Inclusion criteria* • Patients aged 18 years and over undergoing elective surgery *Exclusion criteria:* • Inability to provide informed consent • Co-enrolment in PROTECT CTIMP comparisons • Previous enrolment to the PROTECT-DIVERSITY comparison
Intervention	Electronic multi-lingual consent forms
Treatment duration	N/A
Follow-up duration	After completion of surgery
End of comparison definition	Completion of surgery for final patient

5. Introduction

5.1 Background and rationale

Perioperative trials are poorly representative of society. It is not possible to test an intervention in the entire population. Instead, clinical trials sample a sub-set of the population and extrapolate findings to other patients. This paradigm relies on unbiased sampling according to specified inclusion/exclusion criteria. However, reporting of key diversity characteristics, like ethnicity and socioeconomic status, is limited and clinical trial results are unlikely to be generalisable to the full population (1). During the COVID-19 pandemic a systematic review found that only 2% of clinicals trials reported ethnicity (2). In perioperative medicine, one third of trials reported ethnicity and over 96% reported sex (3-4). However, less than half analysed the results according to sex and only 4% considered ethnicity. Patients say that barriers include burdensome follow-up and consent processes, which are often only written in English (5).

The lack diversity in clinical trials is an important issue, which limits external validity. Trial samples are commonly biased by protected characteristics, including age, sex, ethnicity and socioeconomic status (4). Ethnic minorities are poorly represented in trials, despite comprising 12.5% of the UK population (6). In perioperative trials, ethnicity is reported in only 33% of cases (3). While 98% of clinical trials report sex (7), only one third report the primary outcome by sex, limiting the relevance of trial results to both sexes (8).

Data efficient platform trials offering an opportunity to increase access to research and remove barriers in participation, thereby improving the diversity of patient participation. However, we don't know whether firstly, patient information and consent forms in multiple languages (and electronic or paper format), or secondly, protected characteristics (diversity) data collected using HES or traditional methods like patient questionnaires or direct questioning are suitable for surgical patients speaking different languages.

6. Study objectives

6.1 Objectives

(a) Compare the impact of using multi-lingual consent forms compared to consent forms in English on the ethnic diversity of patients included in the study.

(b) Compare the accuracy and completeness of protected characteristics data collection (age, sex, ethnicity, partner status, disability, pregnancy status, religion, sexual orientation and gender reassignment) using different methods (HES, electronic questionnaires, direct questioning).

6.2 Outcome measures

- Primary outcome: Reciprocal diversity index for ethnicity on a scale of 0 to 100 (9)
- Secondary outcome:
    - Completeness of data collection for protected characteristics.
    - Degree of agreement for protected characteristics data between data collection modalities.

6.3 Study setting

Surgical services of NHS hospitals.

7. Study population

7.1 Inclusion criteria

- Patients aged 18 years and over undergoing elective surgery

7.2 Exclusion criteria

- Inability or refusal to provide informed consent
- Co-enrolment in PROTECT CTIMP comparisons
- Previous enrolment to the PROTECT-DIVERSITY comparison

8. Study Design

Multi-centre, open-label, randomised intervention study.

9. Study procedures

9.1 Target accrual

532 patients aged 18≥ years undergoing elective surgery will be recruited in NHS hospitals.

9.2 Informed consent procedures

The method of informed consent will use either an electronic or paper method, which is consistent with the PROTECT master protocol. For this comparison, the initial mode of consent (electronic or paper) will be determined at random before approaching the patient, which includes consent for entry into the platform. Since the intervention in question is the process of consent, it will not be possible to obtain consent before the 'intervention' i.e. the consent process. In this case, there will be a waiver of consent to randomise to intervention or usual care. After randomisation, the patient will complete the consent process using either multi-lingual consent documents (presented initially in electronic format, but available in paper format) or consent documents in English only (presented initially in electronic format, but available in paper format), according to group allocation. This

process supersedes the procedure for timing of informed consent as detailed in the PROTECT master protocol on “Informed consent procedures”, which will apply to consent for inclusion in the PROTECT platform (master protocol) and this comparison. Intervention group consent materials will be translated into Polish, Romania, Panjabi, Urdu and Portuguese, which are the five most common languages for people where English/Welsh is not their first language. Translations will be undertaken by an approved/certified provider.

The PI has overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki. The PI may choose to appoint a sub-PI to lead local delivery of the PROTECT-DIVERSITY comparison. Any responsibilities of this role will be described on the delegation log. All procedures including data collection, including linkage to routine NHS datasets, will commence as soon as informed consent has been obtained.

9.3 Participant screening

Potentially eligible participants will be screened by the direct care team for entry into the study in accordance with the PROTECT master protocol. Research delivery staff embedded within NHS trusts should be regarded as part of the direct care team. Research is a routine part of effective healthcare and will be subject to the same information governance requirements in this respect. Research delivery staff will therefore be able to screen operating theatre lists, electronic patient records, etc for eligible patients.

9.4 Schedule for each visit

Visit	Screening	Before surgery	After completion of surgery
Eligibility	x		
Randomisation		x	
Informed consent		x	
Demographics		x	x
Review of medical notes		x	x
Follow-up			x

9.5 Randomisation procedures

9.5.1 Randomisation method

Randomisation will occur immediately prior to the approach for informed consent. Participants will be randomised 1:1 to electronic or paper consent using block randomisation with randomly permuted blocks of four participants.

9.5.2 Randomisation procedure

The code creating the randomisation sequence will be prepared by the statistician for this comparison. The allocation sequence will be concealed using sealed envelopes, which will be prepared for each participating site by the statistician for this comparison.

9.6 Study intervention

Intervention

Consent materials available in English (and Welsh for sites in Wales), Polish, Romanian, Panjabi, Urdu and Portuguese, with translation/interpretation available according to local hospital policy. The preferred consent format is electronic, but paper documents will be available.

Usual care

Consent materials available in English (and Welsh for sites in Wales), with translation/interpretation available according to local hospital policy. The preferred consent format is electronic, but paper documents will be available.

9.7 Study assessments

There will be no additional data collection in addition to that defined in the master protocol.

Specific variables of interest include (but are not limited to): Age, sex at birth, ethnicity, partner status, disability, pregnancy status, religion, sexual orientation, gender reassignment, socioeconomic status.

Supplementary forms

Diversity and Inclusion Survey (DAISY) in addition to that specified in the PROTECT master protocol.

9.8 Data collection

Data used for this study will be collected from participants medical records, questionnaires and direct questioning of participants. This information will be entered into the PROTECT database.

9.9 Follow-up procedures

To minimise bias, as much as possible, follow-up data will be collected by an investigator who is unaware of the study group allocation.

9.10 Participant withdrawals

Patients' decision to withdraw from the study will be respected. Please follow the procedures documented in the PROTECT master protocol section "Participant, study and site discontinuation".

9.11 End of study definition

This is defined as when the last participant has completed their surgery.

10. Assessment and management of risk

This is a very low-risk study. There will be no change to clinical care. The intervention under investigation is the mode of consent for research.

11. Statistical considerations

11.1 Sample Size

532 patients

11.2 Statistical design and method of analysis

The primary analysis will use a two-tailed t-test for difference in mean Reciprocal Diversity Index (RDI) and confidence interval, presented using heat maps and/or bar charts. RDI is a measure of the diversity of a community and is commonly used in ecological analysis. Secondary outcome data will be presented as n (%) stratified by data collection modality. Completeness of data collection will be tested using Chi-squared. Agreement between data collection modalities will use intra-class correlation coefficient (ICC) with a two-way random effects model measuring absolute agreement between modalities for each protected characteristic, presented as ICC with a 95% confidence interval (10). A full statistical analysis plan will be developed prior to final analysis of this comparison. A total sample size of 250 participants will give 99% power to detect a difference in RDI of 1.0 from a population mean value of 5.14, and 94% power to detect a difference in proportion recruited from 0.2 to 0.4, assuming a type one error rate of 5%.

12. Ethics

Annual progress reports will be sent to the REC and Sponsor on the anniversary of the favourable opinion for this comparison.

13. Public and Patient Involvement (PPI)

Evidence suggests that clinical trials are poorly representative of society and that the results of clinical trials may not be widely applicable to all patients. Our patient panel highlighted this as a particular cause for concern and were highly supportive of research to understand and improve diversity within clinical trials. Our patient representatives welcomed the use of routinely collected NHS data and patient questionnaires administered via text message or email to collected follow-up data and reduce the burden of patient visits for clinical trials.

14. Data handling and record keeping

Please refer to the PROTECT master protocol section “Data management” for further details.

15. Safety reporting

Due to the nature and design of this study, safety reporting of adverse events will not occur for this comparison.

16. Monitoring and audits

Please refer to the PROTECT master protocol “Monitoring, audit and inspection section” for further details.

17. Study committee

Please refer to the PROTECT master protocol “Study committees” section for further details.

18. Finance and funding

This comparison is funded by the Academy of Medical Sciences and The British Journal of Anaesthesia. The funders will play no role in study design, conduct, data collection, data analysis, reporting or interpretation of the results.

19. Indemnity

Please refer to the PROTECT master protocol “Indemnity/ insurance” section for further details.

20. Dissemination of research findings

Details of the dissemination plans for this comparison can be found in the PROTECT master protocol.

21. References

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