North Bristol NHS Trust

Reducing Repeat **Pl**eural Biopsies **I**n Suspected **Ca**ncer – a study of the TARGET trial cohort comparing the diagnostic yield of standard histology vs additional tests in suspected pleural malignancy

REPLICA

RESEARCH REFERENCE NUMBERS

IRAS Number:	329574
ISRCTN Number / Clinical trials.gov Number:	TBC
SPONSORS Number:	5476

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Chief Investigator:

Signature: .....

Date: ...../...../.....

Name: (please print):

.....

KEY TRIAL CONTACTS

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key Investigator	Dr Anna Bibby, Academic Respiratory Unit Level 2, Learning and Research Building Southmead Hospital Bristol BS10 5NB Tel: 0117-4148049 Email: anna.bibby@bristol.ac.uk
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Sponsor	Research & Development, North Bristol NHS Trust Level 3 Learning & Research Building Southmead Hospital Bristol BS10 5NB
Funder(s)	Southmead Hospital Charity
Clinical Trials Unit	n/a
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Study delivery Group	Dr Geraldine Lynch Dr Nidhi Bhatt Jenny Symonds

i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

BAP1 BRCA-associated protein 1

CA	Competent Authority
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CRF	Case Report Form
FEV1	Forced expiratory volume in 1 second
FISH	fluorescence in situ hybridisation
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IHC	Immunohistochemical
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MDT	Multi-Disciplinary Team
MTAP	methylthioadenosine phosphorylase
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PET-CT	Positron Emission Tomography CT
PPI	Patient and Public Involvement
PM	Pleural Mesothelioma
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

iii. TRIAL SUMMARY

Trial Title	Reducing Repeat Pleural Biopsies In Suspected Cancer – a study of the TARGET trial cohort	
Internal ref. no. (or short title)	REPLICA	
Trial Design	A UK based multicentre study to evaluate whether performing additional diagnostic tests in non-diagnostic pleural biopsies could increase the diagnosis rate in suspected pleural malignancy. Standard pathway vs proposed (involving additional diagnostic tests) pathway	
Trial Participants	A study of the 59 participants who enrolled in the RCT TARGET study at 8 UK sites between September 2015 and September 2018. Inclusion criteria included suspicious pleural thickening on CT scan, non-diagnostic pleural biopsy and MDT decision to perform further CT-guided biopsy to pursue a diagnosis.	
Planned Sample Size	59 participants were enrolled in TARGET. Total sample size is 118, as each participant provides matched data for both standard and proposed pathways. 129 biopsy samples available in total.	
Follow up duration	12 months (already completed as part of TARGET trial)	
Planned Trial Period	12-18 months total	
	Objectives	Outcome Measures
Primary	Identify patients for whom additional pathological testing would have yielded a definitive diagnosis on baseline biopsy, avoiding the need for further invasive tests	Identification of malignancy on biopsy (binary; diagnostic *vs* non-diagnostic) via: i) histopathological confirmation on standard testing *or* ii) histopathological features of PM with demonstrated BAP1, p16 or MTAP deletion *or* iii) Multi-disciplinary Team (MDT) diagnosis
Secondary	i) Investigate whether additional pathological testing would have shortened the overall time to diagnosis and ii) Investigate whether additional testing would have reduced costs	i) Total number of biopsies required ii) Time to diagnosis iii) Stage at diagnosis iv) Number of MDT discussions required v) Biopsy-associated costs vi) Biopsy-related adverse events

	iii) Identify participants who ultimately received a clinico-radiological diagnosis, i.e. no tissue diagnosis was made, in whom additional testing would have provided a definitive diagnosis	l. Overall survival (from first biopsy)

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Southmead Hospital Charity Southmead Hospital Bristol BS10 5NB Tel: 0117 414 0170	Research grant
NBT NHS Trust	Salaries for Dr Geraldine Lynch, Emma Tucker, Dr Nidhi Bhatt, Anna Morley
NIHR	Salary for Dr Anna Bibby
University of Bristol	Salary for Nick Maskell
University of West of England	Salary for Paul White

v. ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor and Funders have no role or remit in the study design, conduct, data analysis and interpretation, manuscript writing or dissemination of results.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Study management group:

Responsible for oversight of the study. It will monitor trial progress, ensure all practical details of the trial are progressing well and feed back to the sponsor. The study management group will be chaired by the CI and will include all members of the named research team. It will meet 4 times during the study period.

Patient and Public Involvement group:

This will involve a specialist nurse and trial co-ordinator communicating details of the trial progress to a group of mesothelioma patients and carers as the study progresses.

Study delivery group:

This involves the people responsible for retrieving histological samples and performing and reporting the pathological tests. They will ensure accuracy and reproducibility of the tests, and updating the investigators on progress.

vii. Protocol contributors

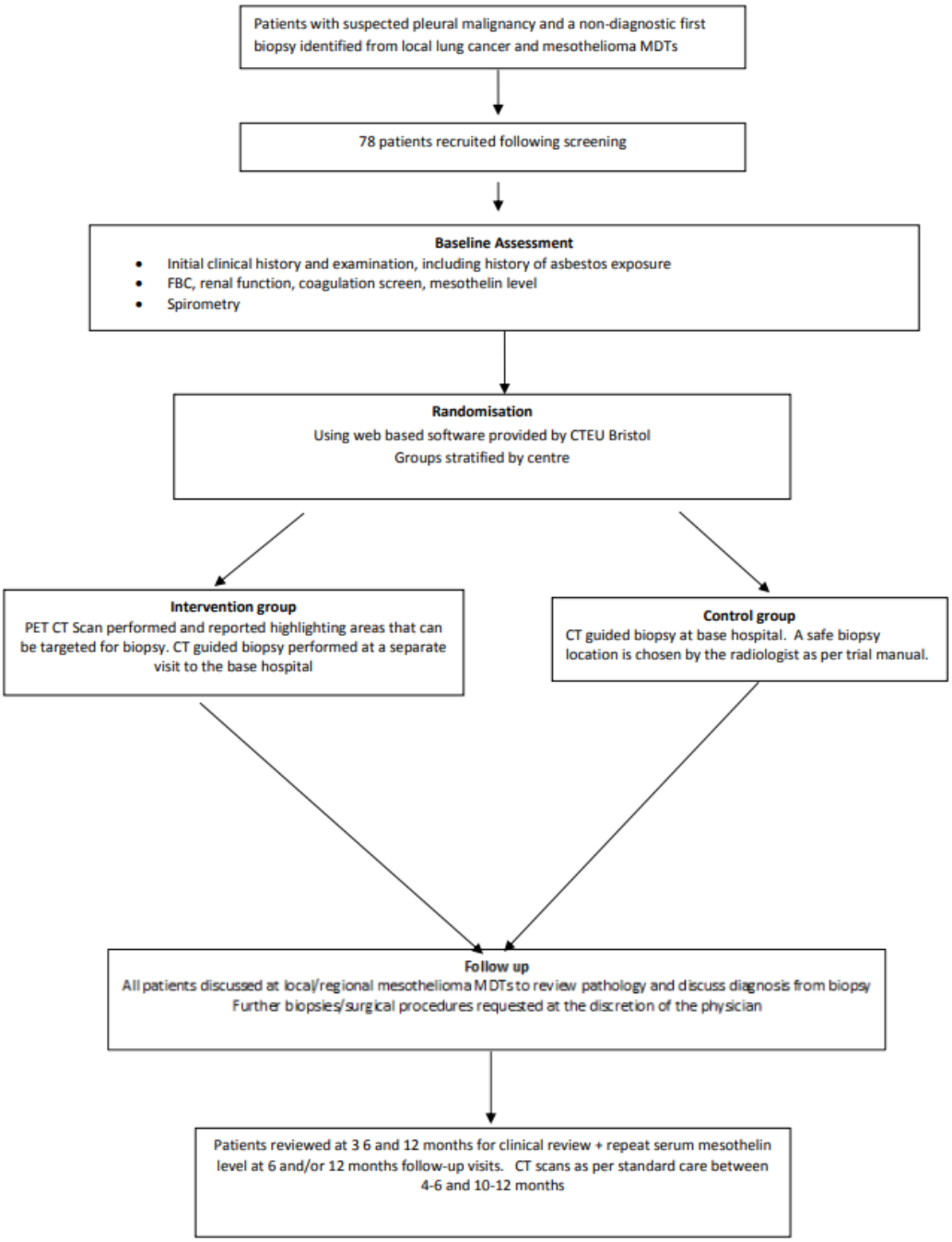
Protocol authors: Geraldine Lynch, Anna Bibby, Nick Maskell, Emma Tucker, Paul White

Study design has involved extensive PPI input. This has led to clarification of terms and gaining further PPI feedback which has resulted in patient-centred justification of study goals.

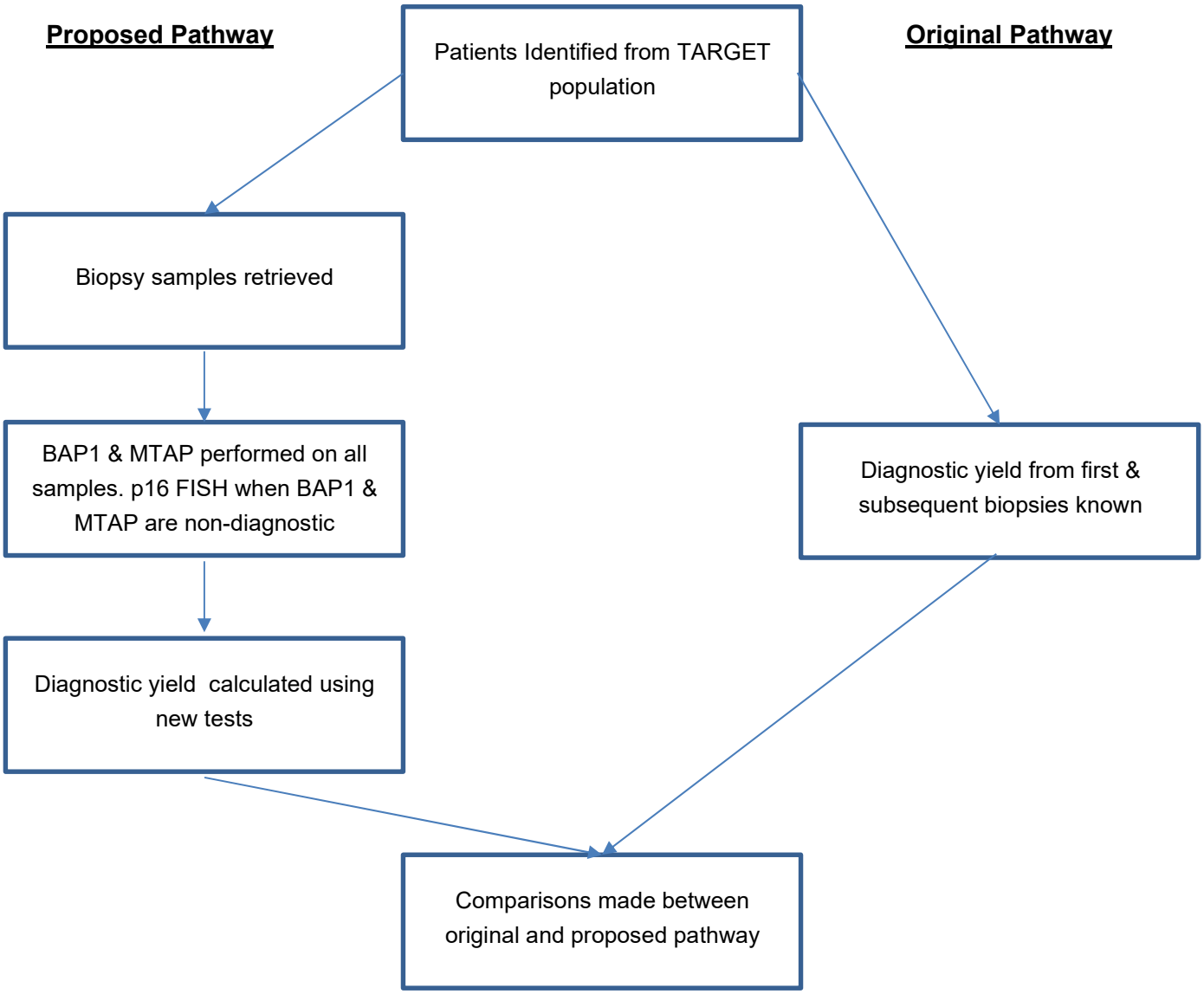
viii. KEY WORDS:	Pleural malignancy, Pleural biopsy, mesothelioma, tumour suppressor gene, multi-disciplinary team, diagnostic yield

ix. TRIAL FLOW CHARTS

TARGET trial flow chart from TARGET trial Protocol version 8, 23/3/18


Patients with suspected pleural malignancy and a non-diagnostic first biopsy identified from local lung cancer and mesothelioma MDTs
78 patients recruited following screening
Baseline Assessment
Initial clinical history and examination, including history of asbestos exposure
FBC, renal function, coagulation screen, mesothelin level
Spirometry
Randomisation
Using web based software provided by CTEU Bristol
Groups stratified by centre
Intervention group
PET CT Scan performed and reported highlighting areas that can be targeted for biopsy. CT guided biopsy performed at a separate visit to the base hospital
Control group
CT guided biopsy at base hospital. A safe biopsy location is chosen by the radiologist as per trial manual.
Follow up
All patients discussed at local/regional mesothelioma MDTs to review pathology and discuss diagnosis from biopsy
Further biopsies/surgical procedures requested at the discretion of the physician
Patients reviewed at 3 6 and 12 months for clinical review + repeat serum mesothelin level at 6 and/or 12 months follow-up visits. CT scans as per standard care between 4-6 and 10-12 months

REPLICA study flow chart:



1 BACKGROUND

Plain English Summary:

Pleural mesothelioma (PM) is a cancer that affects the outside lining of the lung, caused by asbestos exposure. The UK has the highest rate of PM in the world, but despite recent treatment advances, average life expectancy remains under a year from diagnosis. Prompt diagnosis is therefore vital.

People with suspected PM usually require a biopsy of the lung lining to confirm the diagnosis, guide treatment and assist with compensation claims. However, some people need multiple biopsies which increases the risk of biopsy-related complications and prolongs the diagnostic process, causing additional stress and anxiety.

Some people with mesothelioma can deteriorate rapidly. A prolonged time to diagnosis could mean the time window in which someone is sufficiently strong to tolerate life-prolonging treatment is missed.

We believe doing additional tests on initial biopsies will increase the chance of diagnosing PM, avoiding repeat biopsies. This will shorten the period of anxious uncertainty and allow patients to start anti-cancer treatment sooner, improving their chances of survival. Reducing the number of biopsies will eliminate the risks associated with multiple procedures and free up space for other patients with suspected cancer, improving their diagnostic pathway as well.

The extra tests – while not genetic tests – look for markers of genetic changes that happen in PM. Genes are the building blocks in every cell of our bodies that make up who we are and how our bodies behave. Some genes work to stop tumours appearing and, if they do appear, stop them growing. PM tumours can stop these protective genes working or make them disappear, which allows the tumour to grow and spread inside the body. The markers affected in PM are called BAP1, p16 and MTAP and we can test biopsy samples for these. If all three have disappeared, then we can make a diagnosis of mesothelioma.

We previously conducted a study of people with suspected PM who required further biopsies as their first biopsy did not diagnose the condition. All patients consented to be in this trial and an application is underway for approval to perform additional tests on the trial samples. We want to re-test their original and follow-up biopsy samples for BAP1, p16 and MTAP to see whether this would have made the diagnosis sooner and removed the need for further biopsies. We will investigate how many biopsies could have been avoided, how much time would have been saved, and what cost-savings this would have offered the NHS.

BAP1, p16 and MTAP are not routinely used in clinical practice and are not available at many hospitals, despite being relatively inexpensive. BAP1 is already available in NBT and MTAP is undergoing set up. The cost of setting up MTAP is between £150-£400.

We hope our research will show how useful these tests are and how much benefit they offer to patients and NHS services, so they can be used more widely in routine care. Ultimately, we expect our research to be included in national guidelines and change clinical practice across the UK and worldwide.

Scientific summary:

Pleural Mesothelioma (PM) is a primary incurable malignancy of the pleural surface, associated with prior asbestos exposure. Median survival is 9-12 months. Chemotherapy offers marginal therapeutic benefit, but combination immunotherapy has shown promise in recent phase III trials. [1, 2]

Diagnosing PM can be challenging. Radiology supports diagnosis but pathological diagnosis is the gold standard. Some patients present with pleural effusions but pleural fluid sensitivity for PM is low. Pleural biopsy has higher diagnostic sensitivity, but this drops with smaller samples and certain histological subtypes [3]. As a result, some patients undergo multiple investigations, with increased risk of complications and delays to treatment initiation.

Our research unit has previously studied potential approaches to enhance the PM diagnostic process. The multi-centre randomised TARGET trial studied whether Positron Emission Tomography CT (PET-CT) directed biopsy improved the diagnostic yield of biopsies in people with previous non-diagnostic biopsies [4]. PET-CT did not improve diagnostic rates and some repeat biopsies were also non-diagnostic, necessitating further invasive procedures.

Recent advances since TARGET have broadened the panel of tests available for PM biopsy samples. Homozygous deletion of the 9p21 locus is one of the most common genetic alterations in PM, affecting a cluster of tumour suppression genes that show diagnostic promise. These are BRCA-associated protein 1 (BAP1), p16 and methylthioadenosine phosphorylase (MTAP) [4, 5].

BAP1 is a tumour suppressor gene that is mutated in 40-60% of PM tumours, causing loss of BAP1 expression. A 2017 meta-analysis showed BAP1 loss had moderate diagnostic sensitivity (area under the curve of 0.72) with 100% specificity, making it an excellent ‘rule-in’ test for PM [6].

P16 deletion occurs in 80% of PM and is demonstrated using fluorescence in situ hybridisation (FISH). Diagnostic sensitivity of P16 FISH is 0.53, but 0.76 if combined with BAP1 testing [7].

FISH is not performed in all laboratories but immunohistochemical (IHC) staining is universally available. IHC expression of the protein product of the MTAP gene has been shown to be an accurate and reproducible surrogate marker for p16 FISH, with 78% sensitivity and 96% specificity for homozygous p16 deletion and is faster and cheaper to run [8]. When used in combination with BAP1, MTAP IHC has 100% specificity and 76.5% sensitivity for differentiating between malignant and benign mesothelial disease [6].

BAP1, p16 FISH and MTAP are used in some UK centres but are not universally available nor routinely recommended in current guidelines [9-11].

2 RATIONALE

This study aims to evaluate the diagnostic benefit of BAP1, p16 FISH and MTAP in suspected PM by re-testing the initial non-diagnostic/negative biopsy samples from TARGET trial participants to evaluate whether the additional tests would have yielded a definitive diagnosis sooner. If we demonstrate that running these inexpensive tests leads to earlier diagnoses and reduces the need for repeat biopsies, wider adoption of this test panel into routine clinical practice will follow. Our research will inform subsequent national guidelines, leading to changes in mesothelioma MDTs across the country. This will benefit patients (through shortened diagnostic pathways) and the NHS (through cost-savings and increased availability of biopsy appointments).

PPI representatives were universally supportive of the study, citing the potential benefits to them of fewer biopsies, reduced waiting time for a diagnosis, reducing stress and worry from non-diagnostic biopsies and reduced anxiety from all these factors.

2.1 Assessment and management of risk

- Patients: no patients are being recruited as part of this study (we are using historic data and stored samples from a previous study where patients consented to their anonymous information being used for future research).
- Data: risk of missing data: there is a risk that some biopsy samples will be insufficient in size to undergo the stains required. In another study that required pulling of much older biopsies, less than 10% of samples were missing.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

This research aims to answer the question: Could testing for BAP1, P16 FISH and MTAP IHC have removed the need for further invasive procedures in patients with suspected PM and an initial non-diagnostic biopsy?

We will address this question via the following objectives:

- Identify participants from the TARGET trial population (n=59)
- Extract historic biopsies (initial and repeat) from NHS pathology laboratories (n=129)
- Perform BAP1 and MTAP on all extracted biopsies. Where this fails to yield a diagnosis, perform additional p16 FISH.
- Identify patients for whom additional testing would have yielded a diagnosis, avoiding the need for further invasive tests (primary outcome).
- Investigate whether additional testing would have shortened the overall time to PM diagnosis (secondary outcome).
- Identify TARGET participants who ultimately received a clinico-radiological diagnosis, i.e. no tissue diagnosis was made, in whom additional testing would have provided a definitive diagnosis (sub-group analysis).

Primary and secondary outcomes, and outcome measures can be found in the study summary table.

4 TRIAL DESIGN

Observational study using historic data and stored samples from a multi-centre randomised controlled trial (TARGET, ISRCTN 14024829), where each participant will act as a case (additional tests applied to stored samples) and an internal control (initial outcomes using standard testing only).

5 TRIAL SETTING

Historic data and stored samples from patients that consented to participate in the multicentre TARGET trial will be retrieved from NHS pathology laboratories and analysed at NBT.

6 PARTICIPANT ELIGIBILITY CRITERIA

All patients recruited for the TARGET study will be included, provided they have sufficient stored biopsy material to undertake the required additional tests.

TARGET eligibility required all of the following to apply:

- Pleural thickening on CT suspicious for pleural malignancy
- Have had any form of pleural biopsy in the last 12 months (either by thoracoscopy or under radiological guidance) which was non-diagnostic for cancer
- Lung Cancer/mesothelioma MDT decision to perform further CT-guided biopsy to pursue a diagnosis

Participants were ineligible for TARGET if ANY of the following applied:

- Unsuitable for a CT guided biopsy (inability to co-operate, lie still for the duration of the biopsy, uncorrectable coagulopathy, inability to tolerate a pneumothorax, severe underlying lung disease [patients with an FEV1 < 35% assessed using simple spirometry])
- Unable to give written informed consent
- Pregnancy or lactation
- Age<18 years
  Pleural thickening not amenable to a radiologically guided biopsy
- Talc pleurodesis in the previous 6 months

7 TRIAL PROCEDURES

7.1 Recruitment

Patients will be identified from the TARGET trial database.

7.2 Consent

All patients in the study consented take part in the TARGET trial. They consented to have their anonymised data used in future research. Patients will have died by the time of this study, therefore we will not be able to obtain additional consent for use of non-anonymised data or biopsy samples. This study therefore requires CAG and ethical approval to access identifiable patient information while processing patient samples, so findings can be linked with clinical outcomes. TARGET consent form enclosed (Appendix 1)

7.3 Data extraction

Baseline clinical information and follow up data from visits at 3, 6 and 12 months will be extracted from the trial database. Where this data is unavailable, it will be sought from medical records. Variables include:

- Baseline demographic data
- Asbestos exposure history
- Relevant medical background
- Biopsy dates and results
- Biopsy method
- Number of biopsies required for diagnosis
- Biopsy-related adverse events
- Histological diagnosis
- Whether diagnosis was tissue based or clinico-pathological.
- Time to diagnosis (from enrolment)
- Stage at diagnosis
- Number of MDT discussions

- MDT outcomes including ultimate MDT diagnosis and date of diagnosis
- Radiological images and reports used during diagnostic period
- Anti-cancer treatment received
- Healthcare utilisation
- Overall survival

7.4 Storage and analysis of clinical samples

Histological samples from TARGET patients are NHS clinical samples and as such are stored in NHS pathology laboratories. They will be retrieved for staining and analysis at NBT laboratories and may be transferred off North Bristol NHS Trust premises to facilitate the undertaking of p16 FISH. A Material Transfer Agreement will be completed for any and all transfers of samples to and from external sites for storage and/or analysis. Following completion of sample analysis they will be returned to the relevant NHS pathology laboratories.

7.5 End of trial

The trial will be completed when all samples have been stained and reported, with all pathology reporting queries answered.

8 Safety reporting

There is no new patient contact, intervention or sampling as part of REPLICA. There is therefore no safety reporting required.

10 STATISTICS AND DATA ANALYSIS

The independent variable is the availability of BAP1, p16 FISH and MTAP testing (binary; available *vs* not available). The primary outcome is identification of malignancy on biopsy (binary; diagnostic *vs* non-diagnostic), with diagnosis defined as i) histopathological confirmation on standard testing or ii) histopathological features of PM with demonstrated BAP1, p16 or MTAP deletion or iii) Multi-disciplinary Team (MDT) diagnosis. It is assumed that confirmation of a malignant diagnosis stops the diagnostic pathway with no additional biopsies required. Any subsequent biopsies for these participants will not be included in the analysis, preventing double-counting. Secondary outcomes include total number of biopsies required, time to diagnosis, stage at diagnosis, number of MDT discussions, biopsy-associated costs, biopsy-related adverse events and survival. Potential confounding variables include age, sex, biopsy method and tumour histology and these will be adjusted for, when possible, in the analysis.

Outcome measures will be tabulated for standard and proposed pathways and compared using descriptive statistics (including the McNemar test). Univariable and multivariable logistic regression will look for an association between the availability of these tests and likelihood of a diagnostic biopsy. The relationship between secondary outcomes and availability of the tests will be evaluated using adjusted and unadjusted regression analyses and time to event analysis (cox proportional hazard model).

Sample Size:

Total number of patients: 59

Total histological samples for analysis: 129 (all participants had multiple biopsies)

Each participant will be assessed as a case (proposed pathway) and as an internal control (standard pathway) generating two groups of 59 = 118 records for inclusion in the study

Sample size is determined by the number recruited to the TARGET study which demonstrated diagnostic sensitivity (without these additional tests) of 30%. A sample size of 118 (59 in each arm) will allow detection of an increased diagnostic rate of 60% with 95% confidence intervals of +/- 8.8% (based on BAP1 loss prevalence of 60%).

On the assumption that the combination of BAP1 and MTAP will increase the diagnostic rate still higher, a sample size of 118 will allow detection of an increased diagnostic rate of 70% with 95% confidence intervals of +/- 8.2% and a diagnostic rate of 80% with 95% CI of 7.2%

11 DATA MANAGEMENT

Anonymised data from the TARGET trial will be extracted and stored in an excel workbook. Lab data will be shared by the lab team in this format. All data, including identifiable data needed to access clinical information will be stored securely on NBT systems.

All essential documents will be retained in accordance with North Bristol NHS Trust's Archiving SOP following the end of a study.

12 MONITORING, AUDIT & INSPECTION

None planned

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, and other relevant documents.

13.2 Peer review

The study proposal has been reviewed by Southmead Hospital Charity and NBT Research Sponsor as part of the funding application process.

13.3 Public and Patient Involvement

In research design:

This project centres around improving the patient diagnostic experience so patients and their carers are integral to the design. Feedback from PPI representatives included narrative descriptions of their personal experiences of the diagnostic process, and how delays have impacted their journeys. They have voiced support for "anything that could improve things, as it's a very stressful time".

Our dedicated PPI group, consisting of patients with mesothelioma, their carers and a MesoUK nurse. met on 13/3/23 and with Geraldine Lynch on 13/11/23. There were extensive discussions about the study design with feedback welcomed from the group. All responders thought felt this research could be useful, supporting and changes in practice that could help future patients. They highlighted the importance of reducing total number of biopsies and time taken to diagnosis, both of which have been included as secondary outcomes. All respondents reported they would be happy for their data and samples to be used in this context, without the need for prior consent.

PPI representatives also reviewed the plain English summary, which was amended in response to their comments and feedback.

In research management:

We have identified a willing patient representative to sit on the project management group. He will contribute to study oversight, be involved in discussions around data analysis and contribute to write

up as an author on the final manuscript. He will be invited to assist with dissemination of results to other PPI partners.

In Dissemination of findings:

Results will be relayed to those through the PPI process so far who have indicated they wish to stay informed. I will create a plain English summary of the findings to ensure accessibility, sharing these with patients and carers via our local mesothelioma patient group and the annual mesothelioma patient and carer conference. We will disseminate results to the public via the Bristol Academic Respiratory and UK pleural Society twitter feeds, through the Meso UK newsletter and Southmead Hospital Charity updates.

13.4 Regulatory Compliance

The study will not commence until a Favourable REC opinion has been received and HRA approval has been granted.

Approval will also be sought from a Confidential Advisory Group (CAG) to access identifiable patient information while processing patient samples, so findings can be linked with clinical outcomes.

13.5 Protocol compliance

Protocol non-compliances are departures from the approved protocol.

- accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
- deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.
- See RI/QMS/SOP/012: R&I Managing Breaches of GCP or the Protocol

13.6 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial

- the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
- the sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

- See RI/QMS/SOP/012: R&I Managing Breaches of GCP or the Protocol

13.7 Access to data, data protection and patient confidentiality

All study documents will be stored securely in an access-restricted environment, accessible only to study staff and authorised personnel. Data will be collected and stored in accordance with the Data Protection Act 1998. Participants' personal data will be treated as strictly confidential. Anonymity of participants will be upheld by recording only participants' study number, initials and date of birth on key study documentation and analysis files. Only authorised study team members will have access to participants' personal data where this is necessary to link participants to their clinical records on clinical systems and for sample retrieval. No study information will be routinely shared with any external third parties. For the purposes of specific analyses, linked anonymised data may be shared. Only data required for each specific analysis will be shared. Any data being shared externally will be transferred securely electronically with password protection.

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management n/a

13.9 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

13.10 Amendments

See RI/QMS/SOP/003 : Research Study Amendments

14 DISSEMINIATION POLICY

14.1 Dissemination policy

The results of this research will be disseminated to patients and carers, fellow mesothelioma researchers and clinicians. Patients will be informed via our local mesothelioma patient group and the annual mesothelioma patient and carer conference. We will disseminate the results to the public via the Bristol Academic Respiratory and UK pleural Society twitter feeds. We will present results to fellow academics at scientific conferences. Clinicians will be informed via the UK Pleural Society state-of-the-art meetings and/or annual update day. The final report will be written up for publication in a peer-reviewed scientific journal, published open-access.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship of any papers produced from this study will be determined by The International Committee of Medical Journal Editors authorship criteria.

15 REFERENCES

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3. Attanoos, R.L. and A.R. Gibbs, *The comparative accuracy of different pleural biopsy techniques in the diagnosis of malignant mesothelioma.* Histopathology, 2008. **53**(3): p. 340-4.
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6. Hida, T., et al., *Immunohistochemical detection of MTAP and BAP1 protein loss for mesothelioma diagnosis: Comparison with 9p21 FISH and BAP1 immunohistochemistry.* Lung Cancer, 2017. **104**: p. 98-105.
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9. Kindler, H.L., et al., *Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline.* J Clin Oncol, 2018. **36**(13): p. 1343-1373.
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16. APPENDICIES

16.1 Appendix 1-TARGET consent form

North Bristol NHS Trust

TARGET Trial: Patient consent form

Trial number

PATIENT NAME

Randomised controlled Trial to compare the diagnostic yield of Positron Emission Tomography Computerised Tomography (PET-CT) TARGETed pleural biopsy versus CT-guided pleural biopsy in suspected pleural malignancy
Chief investigator: Dr Nick Maskell
Local PI: <insert local PI>

		Please INITIAL each box
1	I confirm that I have read and understood the patient information sheet dated...../...../..... (Version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered to my satisfaction.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my future medical care or legal rights being affected as a consequence.	
3	I understand that sections of my medical notes, and data collected during the study, may be looked at by individuals involved in the running of the trial, by regulatory authorities, or by representatives of North Bristol NHS Trust (NBT) or Clinical Trials and Evaluation Unit (CTEU) Bristol. I give permission for these individuals to have access to my records where it is relevant to my taking part in the research.	
4	I give permission for radiological images obtained during my period of trial involvement and for my trial data (some of which may identify me) to be transported from my hospital site to the sponsor site NBT and the trial co-ordinating centre CTEU Bristol, for the purposes of analysis, monitoring and follow up.	
5	I give permission for anonymised information collected about me on this study to be used for future research.	
6	I give permission for information about me, held by the NHS, to be used to help provide information about my health status and to help contact me if necessary.	
7	I give permission to be contacted by members of the trial team by telephone, or by other means such as text or email, regarding the above study. I understand that my contact details will not be made available to any third parties.	
8	I would like my GP to be notified about my participation in the study and I give my permission for you to contact them.	
9	**I agree to take part in this study.**	

		DD	MM	YYYY
Patient name (please PRINT)	**Signature**	**Date**		

		DD	MM	YYYY
Researcher completing form	**Signature**	**Date**		

3 copies: original for recruiting centre trial file, 1 to patient and 1 for notes

TARGET Consent form Version 3.0 21/10/2016

16.6 Appendix 6 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.