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A trial of OK-432 administered into the chest cavity via an indwelling pleural catheter in people with mesothelioma

Submission date
04/12/2017

Recruitment status
No longer recruiting

Registration date
05/12/2017

Overall study status
Completed

Last Edited
05/10/2022

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Mesothelioma is an aggressive cancer that affects the outside lining of the lung, called the pleura. It is incurable, and there is only one effective chemotherapy (anti-cancer drug) treatment available. This chemotherapy extends life by just three months on average. It is crucial that we find new treatment options that can be offered to people with this disease.
There are lots of new treatments being developed for other cancers that focus on the immune system (the organs and processes of the body that provide resistance to infection and toxins). A healthy immune system is able to identify and attack cancer cells within the body. However, mesothelioma hides from the immune system by reducing the number of protective immune cells in and around the pleura. People with mesothelioma who can overcome this and maintain lots of immune cells in the lung lining seem to live longer.
It has been noticed that patients with mesothelioma live longer after having an infection in the pleura. We think this is because the infection “wakes up” the immune system that was suppressed by the mesothelioma. Immune cells move to the lung lining to attack the infection, and are able to attack the mesothelioma at the same time.
This study aims to use two bacterial agents to mimic infection and stimulate the immune system to attack the mesothelioma. If this is effective, it may help people live longer with mesothelioma. The first agent is called OK432, and is a dead bacteria. The second agent is called BCG, it is a vaccine against the tuberculosis bug, that is also used to treat early bladder cancer.
We use a research design that aims to copy real life clinical care (called the ‘trial within a cohort’ design), to see whether it can be used in larger mesothelioma trials.

Who can participate?
Adults with lung cancer taking part in the ASSESS-meso cohort study

What does the study involve?
From a study called ASSESS-meso, 24 people are identified who are suitable to join TILT, and 16 of these participants are randomly chosen to receive a single dose of either OK432 or BCG, delivered directly into the pleura via an indwelling catheter. The rest of the participants in ASSESS-meso are not told about OK432 or BCG, because in real-life, doctors only tell patients

about treatments if and when they are going to receive them, and not if they are not going to receive them. This prevents participants becoming disappointed or disheartened with their treatment.
All participants are followed up with the same tests. Participants who don't receive OK432 or BCG will act as a comparison group for the people who do, having given their consent for their information to be used in this way when they first joined ASSESS-meso. At the end of the TILT trial we assess various practical issues relating to the trial, e.g. how long it took to recruit participants, how many people agreed to receive OK432 or BCG and how many people completed the trial. At the end of the trial we also interview some of the participants and their relatives to ask what it was like to participate in the trial, whether they had any problems with it, and what could be done differently in future. We hope to gain insight into people's experiences of the trial that will help us make future trials acceptable and attractive to participants.

What are the possible benefits and risks of participating?
By taking part participants are helping us answer an important question as to whether a larger trial of intra-pleural immunotherapy is possible. If we do proceed to a larger trial, this research will help us design it. Ultimately, we hope to find out whether intra-pleural immunotherapy could slow tumour growth in people with mesothelioma.
The risk of side effects from OK432 or BCG is a potential risk. The most common side effects from both medicines are pains in the chest, fevers and feeling tired and achey (flu-like). These side effects usually occur a day or so after the medicine has been administered, and usually get better of their own accord within 2 or 3 days. These symptoms are usually mild and can be managed with over-the-counter treatments such as paracetamol. More serious side effects include infection in the chest, or elsewhere in the body, either due to BCG or other bacteria. Extremely rare side effects include severe allergic reactions (anaphylaxis) and inflammation of the lungs, liver or kidneys. All participants in the trial are closely monitored for side effects, and given treatment as required.
Another disadvantage is the time and energy that is required to complete the three trial visits. Participants need to have additional blood tests as part of the trial. These may be painful or uncomfortable.
As part of the trial, participants undergo 1 extra CT scan and 1 extra chest x-ray that they would not have had otherwise. X-rays and CT scans are associated with ionising radiation that can cause damage to cells in the body and cause them to turn cancerous. This usually takes many years to occur. The amount of extra radiation that participants are exposed to during this trial is equivalent to 4 years' worth of natural radiation exposure.

Where is the study run from?
1. Southmead Hospital Bristol (UK)
2. Churchill Hospital Oxford (UK)

When is the study starting and how long is it expected to run for?
September 2016 to March 2019

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Dr Anna Bibby (Scientific)

Contact information

Type(s)
Scientific

Contact name
Dr Anna Bibby

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Additional identifiers

EudraCT/CTIS number
2016-004727-23

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
34338

Study information

Scientific Title
A Trial of Intra-pleuraL bacterial immuno-Therapy in mesothelioma (TILT): A feasibility study using the ‘trial within a cohort’ methodology

Acronym
TILT

Study objectives
Is it feasible to undertake a three-armed trial within a cohort (TwiC) of intra-pleural immunotherapy in MPM and is it acceptable to participants and relatives?

Ethics approval required
Old ethics approval format

Ethics approval(s)
South West - Central Bristol, 02/05/2017, ref: 17/SW/0080

Study design

Randomised; Both; Design type: Treatment, Drug, Immunotherapy, Qualitative

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Specialty: Cancer, Primary sub-specialty: Lung Cancer; UKCRC code/ Disease: Cancer/ Malignant neoplasms of respiratory and intrathoracic organs

Interventions
This project investigates intra-pleural bacterial immunotherapy in MPM using the Trial within a Cohort (TwiC) methodology. Participants are recruited from an existing observational cohort (the ASSESS-meso study). 24 eligible participants are identified from the cohort, of whom 16 participants are randomly selected to be offered either OK432 or BCG. Randomisation is minimised by WHO performance status (0 vs ≥1) and tumour sub-type (epithelioid/cytological diagnosis versus non-epithelioid).
The intervention (either OK432 or BCG) is delivered intra-pleurally as a single dose via an indwelling pleural catheter. Participants are followed up at four trial visits over 12 weeks. On completion of the trial they return to standard follow up in the ASSESS-meso cohort study. Outcome data of participants in the intervention arms is compared with data from 8 control participants from ASSESS-meso. Qualitative interviews are be undertaken at the end of the trial to assess acceptability of the methodology to participants.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
OK-432 (Picibanil)

Primary outcome measure
Feasibility is assessed using the following feasibility targets:
1. Recruitment rates to time & target >66%, i.e. 18 participants in 12 month recruitment window, or 24 participants in 18 months. This will be assessed using screening and recruitment logs at 12 months and end of trial.
2. Attrition rate of <20%, assessed from participant withdrawal forms at end of trial (nb this

relates solely to attrition due to loss to follow up or participant withdrawal, it does not include attrition due to participant death)
3. Data completeness rates >90% assessed using the trial database at end of trial

Secondary outcome measures
1. Acceptability of the TwiC methodology, explored at qualitative interviews at week 12
2. Acceptability of the intervention (OK432 & BCG), assessed during qualitative interviews at week 12, and by reviewing randomisation logs at the end of trial to determine how many participants were offered the intervention but declined to receive it
3. Safety of intra-pleural OK432 or BCG assessed continuously throughout the trial using patient notes and AE reporting, and tabulated at end of trial
4. Tumour response rates, measured on CT chest at baseline and week 12 using modified RECIST criteria
5. Progression-free survival rates at week 12, measured using modified RECIST criteria on CT chest alongside survival status obtained from patient notes
6. Patient-reported chest pain and breathlessness, measured on visual analogue scales (VAS) at baseline, week 3, week 6 and week 12
7. Patient-reported quality of life, measured using the EQ-5D-5L health questionnaire at baseline, week 3, week 6 and week 12
8. Pleurodesis rates, defined as pleural fluid drainage of less than 50ml on 3 consecutive occasions, with <25% opacification on CXR or <250ml pleural fluid on thoracic ultrasound scanning (TUS) assessed from IPC drainage diaries baseline, week 3, week 6 and week 12
9. Biomarker response, assessed using serum mesothelin blood tests at baseline, week 3, week 6 and week 12
10. Immunological response (BCG arm only) assessed using Mantoux skin testing at baseline and week 6

Overall study start date
01/09/2016

Completion date
31/03/2019

Eligibility

Key inclusion criteria
1. Histological or cytological diagnosis of MPM
2. Enrolled in ASSESS-meso cohort study and has given consent to undergo randomisation for future trials
3. IPC in situ that has drained more than 50ml of fluid on previous 3 drainages OR willing to have an IPC and has a pleural effusion suitable for IPC insertion
4. No chemotherapy in preceding 4 weeks and none planned in subsequent 4 weeks
5. Performance status ≤2, or PS 3 and felt clinically suitable for trial
6. Predicted survival ≥12 weeks from enrolment
7. Able to give written informed consent & meet trial requirements

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 24; UK Sample Size: 24

Total final enrolment
12

Key exclusion criteria
1. No indwelling pleural catheter (IPC) in situ, and has contra-indication to IPC insertion
2. Clinico-radiological diagnosis of mesothelioma
3. Trapped lung with < 50% pleural apposition on x-ray
4. Moderately heavy or heavily loculated pleural effusion
5. Known immunodeficiency or immuno-suppressive medication
6. Intercurrent infection (pleural or elsewhere) or clinical signs of sepsis
7. Known sensitivity or allergy to OK432 or penicillin
8. Previous treatment with immunotherapy
9. Currently enrolled in any other interventional clinical trial
10. Brain metastases or CNS involvement of mesothelioma
11. Pregnancy or lactation, current or planned during the study period
12. Age < 18
13. Any other factor that, in the opinion of the Chief Investigator, would mean participation in the study would be contraindicated

Date of first enrolment
02/01/2018

Date of final enrolment
05/01/2019

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Southmead Hospital
North Bristol NHS Trust
Bristol
United Kingdom
BS10 5NB

Study participating centre

Churchill Hospital
Oxford University Hospitals NHS foundation Trust
Oxford
United Kingdom
OX3 7LE

Sponsor information

Organisation
North Bristol NHS Trust Research & Innovation Department

Sponsor details
3rd Floor L&R Building, Southmead Hospital
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BS10 5NB

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/036x6gt55

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Publication of two papers in high-impact peer-reviewed journals is planned for March 2020, one reporting the quantitative trial results, and one reporting the qualitative research findings. Plan publication of the protocol in a peer-reviewed journal.

Intention to publish date
31/03/2020

Individual participant data (IPD) sharing plan
Anonymised individual patient data can be made available for secondary research (please contact anna.bibby@bristol.ac.uk) once the study has been completed and final trial report published (likely March 2020), conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Thesis results		01/06/2020	12/01/2022	No	No
Plain English results		12/05/2022	17/05/2022	No	Yes
Preprint results		09/07/2021	17/05/2022	No	No
Results article		03/09/2022	05/09/2022	Yes	No
Protocol file	version 3.11	07/03/2019	05/10/2022	No	No
HRA research summary			28/06/2023	No	No