AZTEC@1 Azithromycin Therapy for Chronic Lung Disease

AZTEC@2 Azithromycin Therapy for Chronic Lung Disease

AZTEC (Azithromycin Therapy for Chronic Lung Disease of Prematurity) Follow up studies: AZTEC@1 and AZTEC@2

IRAS ID: 270464

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Trial Summary.

Throughout the world, every year more than 12 million babies are born prematurely, with especially those born at <32 weeks of pregnancy being at risk of developing breathing problems. Our AZTEC study is investigating 796 babies born <30 weeks of pregnancy to determine if a ten-day treatment course with azithromycin, an antibiotic, can decrease the breathing disorder called CLD (chronic lung disease of prematurity) when compared to dummy (placebo) medicine. We have shown that the microbe, *Ureaplasma*, can lead to development of CLD. Azithromycin is very effective against *Ureaplasma,* but also against lung inflammation, which we have shown to be common in premature babies who develop CLD. We shall address the following questions:

1. Does azithromycin improve the long-term respiratory outcomes of preterm-born children at 1 and 2 years of corrected age?
2. Does azithromycin improve (or worsen) the long-term neurodevelopmental outcomes of preterm-born children at 1 and 2 years of corrected age?
3. Does azithromycin reduce the number of hospital admissions in the first and second years of life?
4. Does azithromycin improve the growth of preterm-born infants in the first and second years of life?

Approximately 600 of the 800 AZTEC babies will survive so we should have sufficient numbers of babies to answer the above questions. To answer the above questions at each time point we will.

<u>1 year of corrected age, follow up</u>

1. We shall contact the parents by mailing them the (a) validated neurodevelopmental and (b) respiratory questionnaires at 1 year of corrected age. In addition, we will ask them for (c) information on hospital admissions and (d) growth of their babies, which are routinely collected from the red book by Health visitors and at follow up at the local neonatal units. If they prefer they will be directed to a secure online site to complete the questionnaires.
2. We shall also contact the local hospitals for data from clinic letters including a) symptoms, b) development, c) growth, d) hospital admissions, and e) medication data which will be collected from the first two years from clinic letters when babies are generally seen at the following corrected ages 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months.
3. We will contact NHS Digital for information on hospital admissions and outpatients attendances.

<u>2 year corrected age follow up</u>

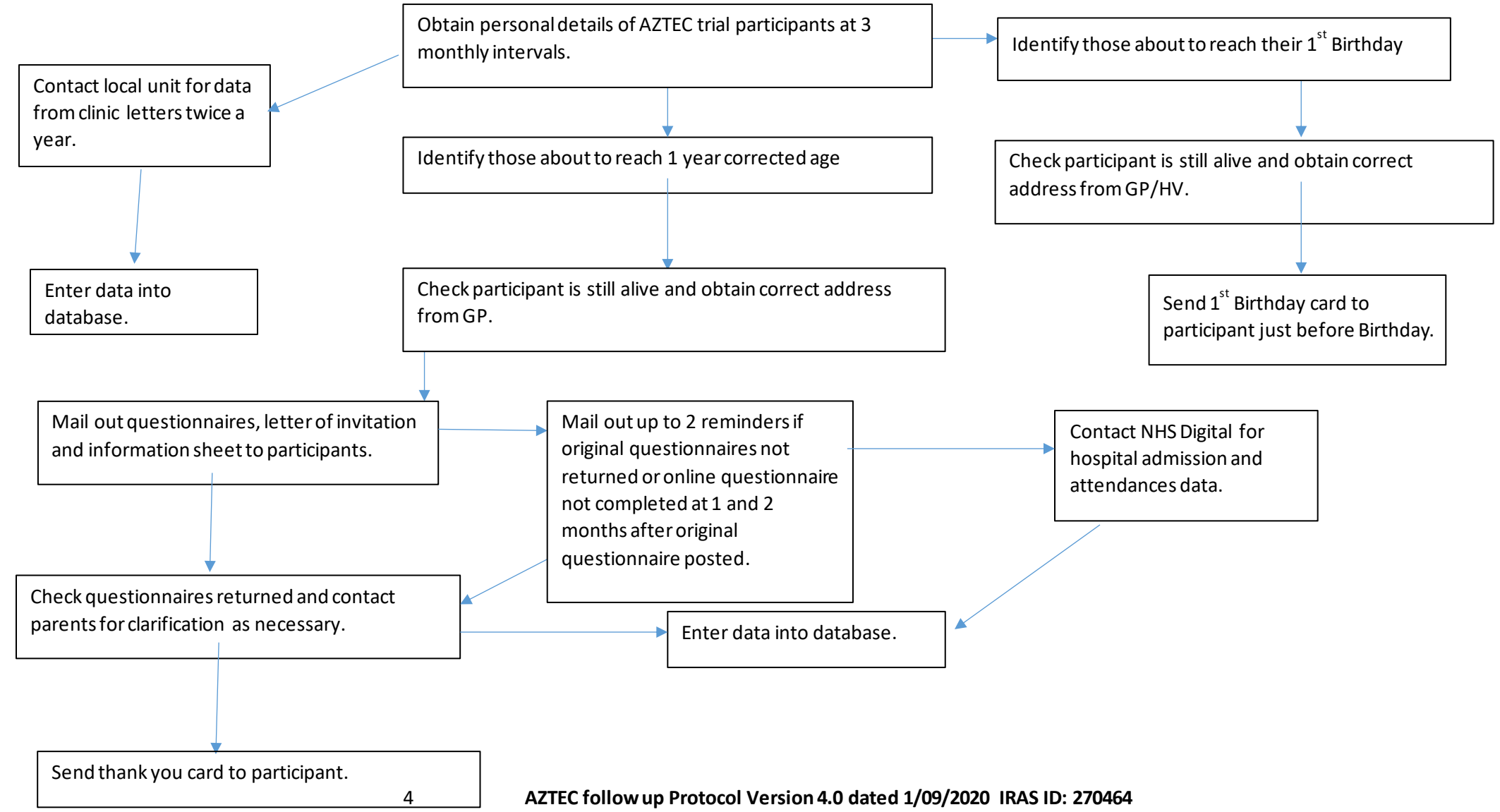
1. We shall contact the parents by mailing them the (a) validated respiratory and neurodevelopmental questionnaires at 2 years of corrected age. In addition, we will ask them for (b) information on hospital admissions and (c) growth of their babies, which are routinely collected from the red book by Health visitors and at follow up at the local neonatal units. If they prefer they will be directed to a secure online site to complete the questionnaires.
2. We will collect neurodevelopmental data from (a) the local units who often see these babies for assessing their development at two years of age; (b) obtain data from a central repository where most of the UK baby units send their data (called NDAU).
3. We shall also contact the local hospitals for data from clinic letters including a) symptoms, b) development, c) growth, d) hospital admissions, and e) medication data which will be collected from the first two years from clinic letters when babies are generally seen at the following corrected ages 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months.
4. We will contact NHS Digital for information on hospital admissions and outpatients attendances.

All the parents are being asked for their permission as part of the consent for the AZTEC to access their baby's data from NDAU, NHS digital and local hospitals and for us to contact them at one and two years of age to be able to answer the above questions. The babies will be aged one between January 2021 and February 2024 (allowing the most premature babies to reach the corrected one year of age) and aged two between January 2022 and February 2025 (revised due to Covid-19 crises resulting in paused recruitment for the main AZTEC trial). The information will be securely stored in a database so we can look for differences for the breathing symptoms and development in children treated with azithromycin comparing the results with those treated with dummy medicine. We shall be able to show if early treatment with azithromycin in premature babies decreases their lung symptoms and developmental problems in the future. We do not anticipate any ethical

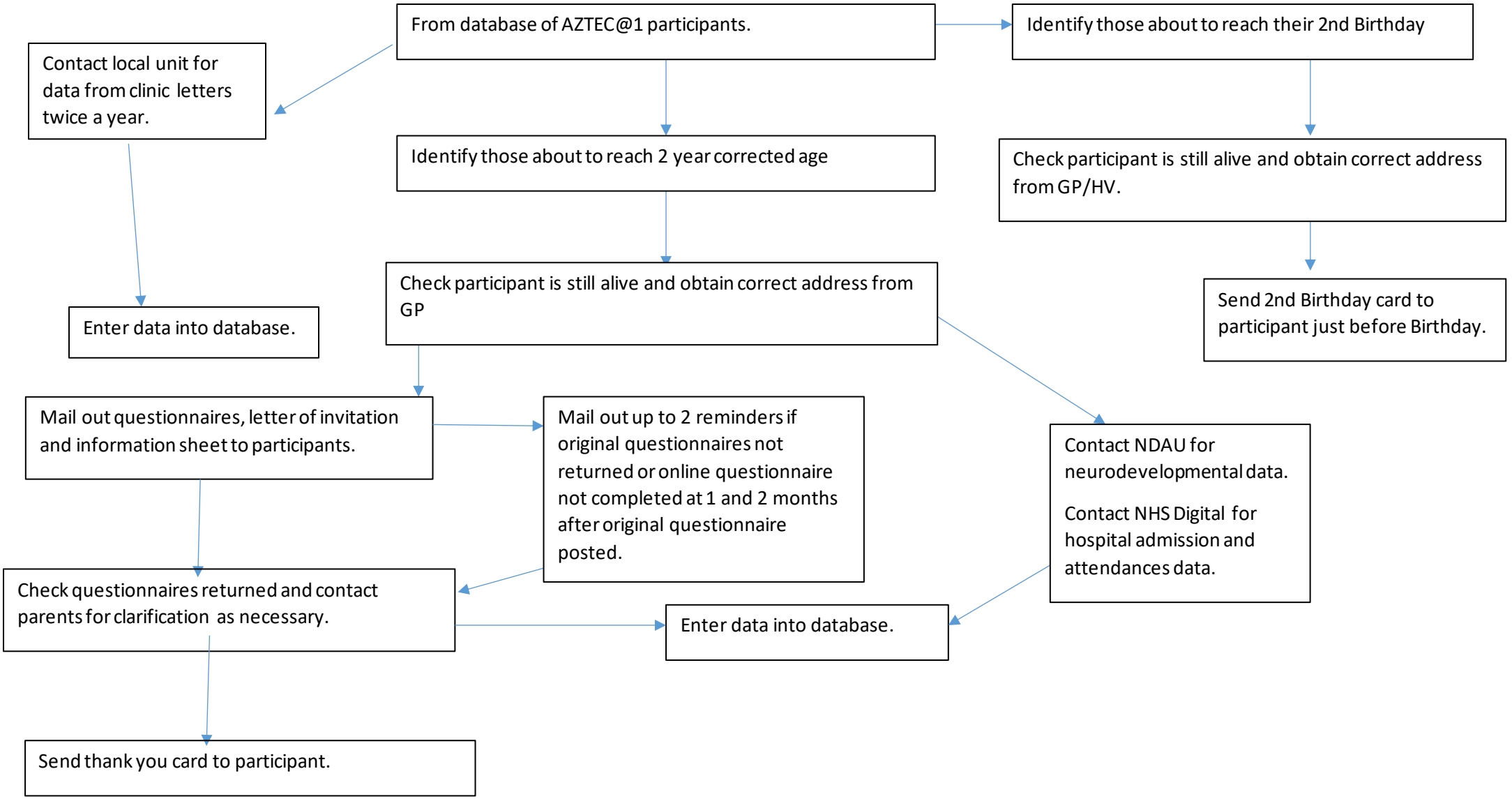
issues besides inadvertently sending a questionnaire to a child who has died. For other studies, we have a plan in place to avoid such an event and also what to do if we do send one to a child who has died. We have avoided this scenario in studies sending >27,000 questionnaires. This project has been reviewed and has full support from parents with premature children. The results of the research project will be presented at national and international meetings and will be published in medical journals, so the results can be shared with other researchers. We shall also share the findings with parents via our website.

Flow Chart

1 year corrected age follow up



2 year corrected age follow up



Background.

- **Respiratory Disorders**

Delivery at an early stage of lung development, and interventions, such as respiratory support with mechanical ventilation and increased oxygen concentrations, commonly lead to respiratory disease. Chronic lung disease of prematurity (CLD) is a major consequence of preterm birth especially in those born at 30 weeks' gestation or less. From 780,000 births in the UK in 2016, ~80 per 1000 were born preterm, ~15 per 1000 were born at <32 weeks' gestation and ~8-10 per 1000 at 28 weeks or less in gestation. From the latter group, approximately a third will be diagnosed with CLD each year, giving an incidence of 480 per 1,000 for that group. A causal factor leading to this morbidity is lung inflammation which peaks at 7 – 10 days of age especially in infants who progress to develop chronic lung disease of prematurity (CLD). [1-5] Whilst the lung injury will resolve in most infants, 30% of infants born at <30 weeks' gestational age develop CLD (most frequently defined as supplemental oxygen dependency at 36 weeks' postmenstrual age). Some will be discharged on home oxygen, with additional associated family, societal and health costs. Interventions to decrease rates of CLD will have economic and health benefits as well as practical and emotional benefits for both the babies and their families. Many factors that are known to cause CLD are not easily modifiable. These include prematurity, mechanical ventilation, oxygen therapy, male sex and patent ductus arteriosus. However, microbial colonisation is strongly associated with the development of CLD [6] and, importantly, is amenable to therapeutic manipulation. A frequent finding in babies who develop CLD is colonisation of the preterm lung with the microbe *Ureaplasma* spp. Our recent meta-analysis confirmed the association between the presence of pulmonary *Ureaplasma* and the development of CLD defined as both supplemental oxygen dependency at 28 days of age (OR 3.04 95% CI 2.41, 3.83) and at 36 weeks' postmenstrual age (OR 2.22 95% CI 1.42, 3.47). [7]

Importantly, as the survival of preterm born babies improves, the longer-term outcomes especially neurodevelopmental, respiratory and growth outcomes are becoming increasingly important to ensure optimal quality of life. However, our systematic review showed that preterm-born children have marked deficits in their lung function especially if they had developed CLD in infancy [8]. In a separate study, we showed for the first time that even babies born moderately preterm are at future risk of developing significantly more lung function deficits than their term-born counterparts. [9]

Since current thinking is that such low attainment of lung function in childhood may be a precursor of developing chronic obstructive pulmonary disease (COPD) in young adulthood, any attempts to ameliorate lung function defects in childhood are to be welcome.

- **Neurological disorders**

Similarly, neurodevelopmental abnormalities are common in preterm-born children: a recent systematic review concluded that "..overall, nearly one out of six and one out of five very preterm or very low birthweight infants had a cognitive or motor delay respectively, assessed with developmental scales at approximately 2 years corrected age and roughly one out of fifteen developed cerebral palsy."[10] Another meta-analysis studying the academic ability of preterm-born children reported lower arithmetic, reading and spelling scores when compared to term controls. In addition, preterm-born children were twice more likely to receive special educational assistance. The review noted that preterm-born children with CLD were particularly at risk of poor academic performance. [11] Another meta-analysis suggested that a risk factor for cerebral palsy was CLD with an OR of 2.10; (95% CI 1.57 to 2.82).[12]

- **AZithromycin ThErapy for Chronic lung disease – AZTEC**

In order to decrease rates of CLD, we have secured funding from the NIHR's Health Technology Assessment (HTA) programme for the AZTEC trial to study 796 preterm babies of <30 weeks' gestation, who require invasive or non-invasive respiratory support for at least two hours at birth, from 25 tertiary neonatal units in the UK, starting recruitment in June 2019 (to December 2021). The primary outcome for the AZTEC trial is to

determine if ten-day treatment with i.v. azithromycin (20 mg/kg for 3 days then 10 mg/ml for 7 days) improves survival without development of physiologically defined CLD when compared to placebo treatment. Azithromycin is increasingly used in respiratory disorders such as cystic fibrosis and COPD (recently reviewed in ref [13]). It is attractive as it is preferentially taken up by lung phagocytic cells such as macrophages, being concentrated approximately 100 times more than in plasma. It has potent actions against both infections (including *Ureaplasma*) and inflammation (especially pulmonary inflammation). *Ureaplasma,* which is strongly associated with the development of CLD, will be sought in tracheal and nasopharyngeal samples and included in the final analyses.

In summary, respiratory disorders and neurological disorders are common in preterm-born babies. They are at risk of future development of respiratory dysfunction in both childhood and adulthood thus any attempts to decrease rates of lung disease are to be welcome. It is likely that interventions will improve, not only short term outcomes but also longer term outcomes as shown by the recent UKOS trial data in childhood.[14] AZTEC will evaluate if azithromycin improves short-term outcomes. This trial provides a unique opportunity to evaluate the longer-term outcomes after early treatment to decrease lung and possibly neurodevelopmental outcomes as discussed below. In addition, if hospital admissions after discharge from the neonatal unit are decreased especially for respiratory reasons this will have huge benefits for the preterm infants themselves and also by cost savings for the NHS.

Why is this research important in terms of improving the health and/or well-being of the public and/or to patients and health and care services?

The AZTEC study is an important study that will assess if the early use of azithromycin decreases short-term improvement in respiratory disease in at-risk babies. However, it will be important to show its safety before clinicians will be comfortable with its routine use in preterm-born babies. Thus, we shall show if neurodevelopmental outcomes at 1 and 2 years of corrected age are affected in the treated group when compared to the placebo-treated group. Secondly, recent evidence suggesting that the early use of azithromycin for only three days seems to improve respiratory symptoms at one year of age in a small proof of principle study provides an excellent opportunity to assess this important outcome in a much larger group of infants recruited by the AZTEC study. Finally, as additional emerging evidence in animal models, as described below, is showing that azithromycin may be efficacious in neurodevelopmental outcomes, serendipitously, with the AZTEC study, we shall also be able to address if a ten-day early treatment course of azithromycin decreases rates of neurodevelopmental abnormalities at one and two years of corrected age. Thus, our study will assess if the treatment has the potential to improve the health and well-being of preterm-born children in the longer term. In addition, it will confirm if the treatment causes harm or, as expected, improves both long term respiratory and neurodevelopmental outcomes, which both will clearly lead to decreased costs to the wider NHS.

Review of existing evidence - How does the existing literature support this research?

Azithromycin has also been studied from a respiratory point of view and since pulmonary inflammation seems to play an important role in the development of CLD and azithromycin is thought to modify inflammation, Ballard performed a pilot double-blind, randomised, placebo-controlled trial specifically excluding neonates colonised by *Ureaplasma* spp.[15] In this study, 45 Infants (birth weight 1000g or less) were randomised to azithromycin treatment or placebo within 48 hours of birth. Mortality, incidence of CLD and other morbidities were not significantly different between groups but this trial was not powered for these outcomes. In a subsequent study, Ballard et al. randomised 211 neonates with birth weight 1,250g or less to azithromycin or placebo irrespective of *Ureaplasma* spp. colonisation status reporting improved CLD rates in *Ureaplasma* spp. colonised infants.[16] The recent meta-analysis by Nair [17] and colleagues reported when pooling the three available studies [15, 16, 18], azithromycin demonstrated a significant reduction in CLD, and also the composite outcome CLD/Death (irrespective of *Ureaplasma* spp. status): respective risk ratios of 0.83 and 0.86. In the trial by Gharehbaghi et al. (n=108), azithromycin showed a reduction in CLD, and in the composite outcome CLD/Death (irrespective of *Ureaplasma* spp. status): 21 (43%) of the 52 participants in the control group and 14 (25%) of 56 in the azithromycin group developed CLD defined as oxygen dependency of 28 days and beyond (p = 0.04). Twelve participants had CLD at 36 weeks postmenstrual age; 9 of which were from the control group (P = 0.04).

For the main AZTEC trial, as discussed above, both pulmonary inflammation and pulmonary colonisation by *Ureaplasma* will be targeted by azithromycin to provide definitive evidence for the role of both in the development of CLD. In particular, our systematic review not only showed increased risk of developing CLD but, using meta-regression, we showed that this was independent of the gestational age of the baby (Figure 1). Furthermore, we had reviewed the literature of the adverse events associated with the use of azithromycin [19] and Nair's systematic review [17] strongly suggest that azithromycin is likely to be efficacious in this group. Whilst it is always important to ensure that the treatment does not result in long term neurodevelopmental abnormalities, two new pieces of evidence have emerged since AZTEC was funded which makes this study a unique, exciting opportunity to pursue these suggestions: firstly, recent evidence from Viscardi et al. presented at the European Respiratory Society in September 2018, suggest improved respiratory morbidity at 12 months of corrected age in *Ureaplasma* positive infants who were treated with 20 mg/kg azithromycin for 3 days in early life (original sample-121 with 44 *Ureaplasma* positive) when compared to *Ureaplasma* positive infants treated with a placebo, providing proof of principle that azithromycin may improve longer term respiratory outcomes.[20] AZTEC provides an important opportunity to investigate if therapy targeting both pulmonary inflammation and infection (especially from *Ureaplasma*) decreases respiratory symptoms at one and two years of corrected age when compared to the placebo group.

Secondly, use of azithromycin may improve stroke outcomes, [21] but its use in the preterm population for neuroprotection is only now being explored in animal neuro-injury models showing improvements in neurodevelopmental outcomes. In an initial study, high dose of 150 mg/kg azithromycin showed neuroprotection in a neonatal rat hypoxic-ischaemic brain injury model. The same authors presented the effects of a more clinically relevant dose of 30 mg/kg in the same model neonatal rat of right carotid ligation with 8% oxygen hypoxic exposure at the Pediatric Academic Societies (PAS) meeting in May 2018. The results convincingly showed that the azithromycin group had (a) less functional defects, (b) less weakness in left paw grip, and (c) less right hemisphere damage, when compared to the placebo groups.[22]

In another presentation at the same meeting, azithromycin was administered at 20 mg/ml for 2 days in a neonatal mouse model of periventricular leukomalacia induced by temporary ligation of both carotid arteries and exposure to 8% oxygen. The treated group showed both physiological (decreased paresis and co-ordination deficits) and histological improvements (decreased ventriculomegaly and neuronal necrosis/apoptosis).[23]

These data are very congruous with our findings: by reviewing the whole of the literature for respiratory outcomes, we showed that preterm-born children and young adults have respiratory deficits especially if they developed CLD in infancy.[8] Another of our systematic reviews reviewing the treatment for the respiratory deficits observed in preterm-born children with respiratory disease was disappointing as only one study investigated the longer term use of bronchodilators although the majority of the 21 studies using a single dose of bronchodilator showed an improvement.[24] Taken together these data and the emerging studies provide an excellent opportunity to assess the effect of azithromycin on longer term respiratory and neurodevelopmental outcomes from the AZTEC study.

What is the research question / aims and objectives?

The following research questions will be investigated:

1. Does azithromycin improve the long-term respiratory outcomes of preterm-born children at 1 and 2 years of corrected age?
2. Does azithromycin improve the long-term neurodevelopmental outcomes of preterm-born children at 1 and 2 years of corrected age?
3. Does azithromycin reduce the number of hospital admissions in the first and second years of life?
4. Does azithromycin improve the growth of preterm-born infants?

Research Plan

It is anticipated that 75% of the initial AZTEC group will survive thus we shall aim to evaluate ~600 surviving

babies from the original cohort. The initial inclusion criteria will be infants born at <30 weeks' gestation, and who require invasive or non-invasive respiratory support for at least two hours at birth; recruited from 25 tertiary neonatal units in the UK between June 2019 and August 2022 (revised timelines recruitment due to Covid-19 crises).

Data Collection

The 1 and 2 year group will be recruited as follows. As part of the initial consent procedure, we shall ask the parents if they are willing for us to contact them to assess both respiratory, growth, admissions to hospital and neurodevelopment at 1 and 2 years of corrected age. We shall collect the data as follows:

1year of corrected age, follow up

1. We shall contact the parents by mailing them the (a) validated neurodevelopmental and (b) respiratory questionnaires at 1 year of corrected age. In addition, we will ask them for (c) information on hospital admissions and (d) growth of their babies, which are routinely collected from the red book by Health visitors and at follow up at the local neonatal units.
2. We shall also contact the local hospitals for data from clinic letters including a) symptoms, b) development, c) growth, d) hospital admissions, and e) medication data which will be collected from the first two years from clinic letters when babies are generally seen at the following corrected ages 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months.
3. We will contact NHS Digital for information on hospital admissions and outpatients attendances

2year corrected age follow up

1. We shall contact the parents by mailing them the (a) validated respiratory and neurodevelopmental questionnaires at 2 years of corrected age. In addition, we will ask them for (b) information on hospital admissions and (c) growth of their babies, which are routinely collected from the red book by Health visitors and at follow up at the local neonatal units.
2. Firstly, (almost) all neonatal units in the UK follow up their at-risk preterm-born population, generally those born at <32 weeks' gestation, until two years of age at which time the children are discharged or referred to the community paediatric team if any issues continue. Almost all units formally assess their preterm population at two years of age with most using the Bayley's 3 test. Data will be collected by liaising with the local teams. Secondly, almost all UK units now use the same BadgerNet system to collate their data which is submitted centrally to the National Neonatal Research database (NNRD) which is based at the National Data Analyses Unit (NDAU) at Imperial College led by Professor Nina Mode and Dr Chris Gale (who is a member of the AZTEC Trials Steering Committee). NNRD is a database which collects data from all the neonatal units in the UK including information on demographics of the babies, records of interventions and treatments throughout the neonatal inpatient stay, information on diagnoses and outcomes, and follow-up health status at age two years. It has a national procedure and regulatory approvals for obtaining data from all the UK units hence is ideally placed to provide the data we require. We have requested access to the data from NDAU via their formal route.
3. We shall also contact the local hospitals for data from clinic letters including a) symptoms, b) development, c) growth, d) hospital admissions, and e) medication data which will be collected from the first two years from clinic letters when babies are generally seen at the following corrected ages 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months.
4. We will contact NHS Digital for information on hospital admissions and outpatients attendances

The modified Liverpool respiratory questionnaire was used successfully in our Respiratory and Neurological Outcomes of children born Preterm Study (RANOPs) for preterm and term-born children to report their respiratory symptoms.[25] The questionnaire has previously been validated and is designed for use in postal surveys children aged less than 5 years of age.[26] Therefore, based on our previous experience and the literature, it will be an ideal tool to obtain the child's respiratory information from the parents.

Up to two reminders to complete the questionnaires will be issued (unless parents specifically request not to be contacted) at the following time points: 1 month and 2 months after the original questionnaire was posted.

Data Analyses

Data will be collated and analysed as follows. All returned questionnaires will be scanned, validated, checked for accuracy and stored in a secure database (Remark Office OMR 8, Gravic, Philadelphia, USA). Remark software was used previously in the RANOPs. We shall check every questionnaire has been scanned correctly into the secure database and enter any additional free text as necessary. In addition we will collate any data using the online questionnaire tool. We will use the following online survey tool https://www.onlinesurveys.ac.uk/.

The following outcomes will be recorded from the questionnaires and from data collected from AZTEC:

1. **Respiratory symptoms** (using modified Liverpool questionnaire), as shown in Table 1 from the RANOPs study.
2. **Neurodevelopmental symptoms** (using the Parent Report of Children's Abilities – Revised for preterm infants (PARCA-R questionnaire) and the Ages and Stages questionnaire)
3. **Number of hospital admissions and reasons for admission.**
4. **Growth of the baby at birth, discharge and 1 and 2 years of corrected age.**

Data analyses will be described in a predefined statistical analysis plan (SAP) and will be analysed using statistical packages including SPSS. Initially, we shall present the results descriptively as shown below in Table 1 for RANOPs.[25] Data analyses will be conducted to study any differences in the respiratory, growth, hospital admission and neurodevelopmental outcomes between the placebo and the treatment group by using two-by-two tables and Chi-square testing. We shall consider $p<0.05$ as significant although mainly report as 95% confidence intervals. We shall also model the data, as in our previous publications, to identify early life factors that may result in long-term respiratory/neurodevelopmental abnormalities and if the treatment effect is influenced by early life factors e.g. gestation, gender, use of mechanical ventilation, etc. Initially. We shall report the uni-variate data with a view to including any relevant factors into a model (using linear or logistic regression as appropriate).

Table 1 Childhood wheezing, family history, inhaler use and hospital admissions for all children less than 5 years-of-age compared by gestational age (unadjusted OR).

	Very Preterm	Moderate Preterm	Late Preterm	Full Term
	N = 502	N = 479	N = 1,130	N = 1,402
Wheeze-ever (%)	325 (64.7%)	266 (55.5%)	581 (51.4%)	571 (40.7%)
OR (95% CI)	2.7 (2.2, 3.3)	1.8 (1.5, 2.2)	1.5 (1.3, 1.8)	
p-value	<0.001	<0.001	<0.001	
aOR (95% CI)#	2.6 (2.1, 3.3)	1.8 (1.4, 2.2)	1.5 (1.2, 1.7)	
aOR (95% CI)^	2.8 (2.2, 3.4)	1.9 (1.5, 2.3)	1.5 (1.3, 1.8)	

The power calculation for the main AZTEC trial is based on a 12% improvement of survival without CLD. For the current study, we shall be restricted to a sample size of ~600 (after allowing for deaths of approximately 25% from the original cohort of 796 infants) and believe we should be able to obtain data for at least 75%, i.e. 450, of the survivors. Recruitment of 450 would permit a very clinically relevant detection of 8.77% and 9.82% difference between the treated and placebo groups at a power of 0.80 and 0.90 respectively, both with a $p<0.05$; whereas recruitment of 600 would provide a difference of 7.71% and 8.68% between the groups at a power of 0.80 and 0.90 respectively both with a $p<0.05$ (Table 2). We are confident of achieving at least 75% of the recruitment especially as the rates of formal neurodevelopment in the UK is constantly improving, currently standing at 63% (2017 data) having improved on a year-on-year basis, especially in tertiary units.

Table 2: Power calculation

Number of children in	Power	p-value	Power to detect difference from expected

total			rate in untreated children
450	0.80	<0.05	8.77%
450	0.90	<0.05	9.82%
600	0.80	<0.05	7.71%
600	0.90	<0.05	8.68%

1. **Ethical issues.** The main ethical consideration is that we need to ensure we do not contact the parents of children who have died especially since discharge. As with RANOPs, we shall put into place methods to ensure as far as possible that this does not occur and our existing standard operating procedure (SOP) will be modified to mitigate the risks and to counsel the parents if such an event occurs. We will contact the child's GP/HV to try to ascertain that the child is still alive. The child's GP will be recorded in the original AZTEC trial and the parent's will be consent to their GP being contacted at the later dates. Consent to take part in the AZTEC follow up study will be obtained in the original AZTEC trial. Parents can choose not to complete the questionnaires. Parents will be advised to contact the study team if they no longer wish to be contacted about the study. If they do not complete the questionnaire at 1 year of age they will still be contacted at 2 years' of age and data will still be collected from the local hospital as we have consent to do so, unless they request no further contact. There are no particular stopping rules for this study as the main AZTEC trial will include robust monitoring of adverse events and will have both a Trials Steering Committee and a Data Monitoring Committee to monitor progress but are not deemed to be necessary for the follow-up study. We shall, however, participate in the Trials Management Group meetings on a regular basis.
2. **PPI.** This and the original AZTEC application have included NG as a parent representative and the original study including later follow up in infancy have been reviewed by parents of preterm-born children who fully supports the project plan. Respiratory outcomes of children born preterm has been extensively studied by our group. Indeed, the RANOPs was a cross-sectional population questionnaire study of both neurodevelopment and respiratory outcomes of over 26,200 (50% preterm- and matched term-born) Welsh-born children aged 1-10 years with >7,000 responses.[27] On the whole the questionnaires were well received by parents and the response rate was good. The current study also had parent involvement in the design and acceptability of the study.
3. **Timelines.** The initial 796 babies will be recruited to the AZTEC study starting in June 2019 until the end of December 2021. The estimated 600 surviving babies, therefore, will be 1-year corrected age between January 2021 and April 2023 (allowing the most premature babies to reach the corrected one year of age) and aged two between January 2022 and April 2024.

Dissemination, Outputs and anticipated Impact

We shall report the effects of early use of azithromycin on later respiratory, growth, hospital admission and neurodevelopmental outcomes of children when compared the placebo group. The findings, regardless of whether they are positive or negative, will be presented to the wider research, clinical and lay communities via formal presentations at national and international meetings and by publication in relevant medical publications. We shall publicise any important findings via our website for AZTEC and via the press if appropriate. We encourage parents to access the findings from our dedicated websites thus will also encourage the same for the AZTEC follow up sudy. We will send Thank You and/or Birthday cards to the parents regardless of their response to both thank them for their incredible dedication and for keeping them engaged for the current and future studies.

Project Management

The project team consists of Dr Sarah Kotecha, post-doctoral research associate (PDRA) who has great experience in cohort studies including analyses for our RANOPs and RHiNO studies. Dr Kathy Jones is the research admistrator and Dr Chris Course, Clinical Research Fellow, will provide clinical expertise on a day to day basis. Professor Sailesh Kotecha is Chief Investigator for the AZTEC studies. We shall work together with the wider AZTEC team who together have a track record in clinical research and questionnaire studies and carrying out timely studies. There will be regular weekly meetings to discuss the progress of the project and to

identify and rectify any issues as soon as they occur as well as monthly TMG meetings to formally assess the progress of both the main study and the follow up element will also be placed as a regular item on the agenda

The confidentiality of the patients involved will be maintained throughout with the aim of ensuring robust security arrangements following our University security policy as we do for other studies such as collation of perinatal death data for the All Wales Perinatal Survey (running between 1993-2018) therefore we very used to working with secure data. All questionnaires and other identifiable data will be stored in a secure fire-proof, double locked location and the database with patient IDs will be saved on secure Cardiff University hard drives. We have experience of working with confidential patient data and are aware of the safe guards which need to put in place.

Ethics

Ethical approval will need to be obtained for this follow on study. Ethical approval has already been obtained for the consent procedure including options to contact the family including mailing of the questionnaires as well as acquiring relevant data from the local units. The main ethical consideration is to avoid contacting parents of a child who has died as far as is humanly possible. Data from infants who die before discharge will be available as part of the outcome measures for AZTEC, but GPs will be contacted to confirm the correct address and survival of the child. Our existing SOP will be updated to mitigate this risk and include the actions undertaken if such an event occurs. For our questionnaire study of >26,000 and for our current RHiNO study currently of >3,200 mailings, we have avoided this eventuality by using robust methods which we hope to also use for the AZTEC follow up study.

Success Criteria

The major criterion is the success of obtaining data for respiratory, growth, hospital admission and neurodevelopmental outcomes for at least 75% of the infants discharged, approximately 450 from the 600 anticipated survivors.

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