NIHR reference No. **135636**

Final Protocol

Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates: a rapid review and early economic analysis

External Assessment Group Newcastle University External Assessment Group,
Population Health Sciences Institute,
Newcastle University, Newcastle upon Tyne, NE1 7RU

Project Leads Dr Nick Meader, Population Health Sciences Institute,
Newcastle University, Newcastle upon Tyne, NE1 7RU,
Email: [redacted]

Dr Hosein Shabaninejad (Health Economics),
Population Health Sciences Institute,
Newcastle University, Newcastle upon Tyne, NE1 7RU,
Email: [redacted]

Project Team Dr Ryan PW Kenny (Lead Reviewer)

Akvile Stoniute (Reviewer)

Dr Tomos Robinson (Health Economist)

Fiona Beyer (Information Specialist)

Hannah O'Keefe (Information Specialist)

Acknowledgements: We thank Dr Marie Westwood, Dr Nigel Armstrong, Caro Noake, Prof Luke Vale, Stephen Rice, and Dr Gurdeep Sagoo for their comments on the draft protocol.

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Plain English Summary

Disease background

Infection is a common cause of serious illness and death in newborn babies receiving intensive care. Infection can develop into sepsis which is a life-threatening response to an infection.

Current practice

About 1 in 2000 newborn babies will experience sepsis. But a larger group with suspected sepsis receive antibiotics.

It is important to start antibiotics within an hour of the decision to treat. Since standard investigations for sepsis take time, antibiotic treatment is often started before receiving test results. The decision to continue treatment can be reviewed once the result comes back from the laboratory.

Aminoglycosides are the first choice antibiotics for treating sepsis in newborn babies. But these treatments can cause hearing loss in some newborns. People with a particular genetic variant called m.1555A>G who receive aminoglycosides are at a very high risk of hearing loss.

Rapid testing to identify m.1555A>G

There are potential benefits to identifying this genetic variant in newborns, or the mother pre-birth as a proxy for the newborn, before aminoglycoside treatment. For example, a different type of antibiotic could be provided to reduce the risk of hearing loss in this group.

Genedrive MT-RNR1 ID Kit is the first point of care test developed to identify m.1555A>G in newborns. The company that developed the test have stated the kit can provide a result in 26 minutes. So, the test has the potential to inform decisions about antibiotic treatment within the recommended start time.

Current diagnostic assessment

This diagnostic assessment will consider whether the Genedrive MT-RNR1 ID Kit has the potential to provide an effective and safe alternative to current practice for initial assessment and monitoring in new-born babies with a suspected infection. In addition, we will identify evidence gaps to support further evidence generation.

1. Decision problem

1.1. Purpose of the decision to be made

Neonates with suspected infection or sepsis are commonly treated with gentamicin, an antibiotic of the aminoglycoside family. These antibiotics are associated with a very high risk of damage to the ear (ototoxicity), including profound bilateral deafness, particularly in people with the *MT-RNR1* gene m.1555A>G mitochondrial genetic variant.[1,2] Estevilli et al.[2] in a study of people with this variant, found a much lower median age for hearing loss (5 years) in those treated with aminoglycosides compared to those not treated with aminoglycosides (20 years). Therefore, identifying the m.1555A>G variant in neonates in need of antibiotic treatment for suspected sepsis has the potential to reduce the risk of early hearing loss in this population.

The purpose of this assessment is to investigate the usage of the Genedrive MT-RNR1 ID Kit in identifying the m.1555A>G variant in neonates with suspected infection or sepsis. In addition, we will assess the usage of this technology for testing mothers of neonates at risk of sepsis to provide an indication of the likelihood that the neonate has this variant.

As antibiotic treatment with aminoglycosides for neonates is recommended by NICE within 1 hour of suspected infection, the availability of rapid genetic testing could be used to optimise antibiotic prescribing. The availability of timely information on the presence of the m.1555A>G variant could reduce rates of aminoglycoside prescribing and hence the incidence of ototoxicity in this group. This assessment will consider existing evidence on whether Genedrive MT-RNR1 ID Kit can reliably identify the m.1555A>G variant in neonates with suspected infection within a one hour clinical window. This assessment will also consider the available evidence, and identify evidence gaps, on how rapid testing for the m.1555A>G variant affects antibiotic prescribing decisions and subsequent clinical effectiveness and cost-effectiveness in identifying neonates with the m.1555A>G variant to aid clinical decision making.

1.2. Place of technology

MT-RNR1 testing is more commonly conducted retrospectively. Although prospective testing is currently used for people who have a predisposition to gram-negative infections. Current genetic laboratory testing varies between different laboratories but may include techniques such as restriction enzyme assay and sequence analysis.

Laboratory testing is estimated to take 2-6 weeks. Such testing is unable to provide results within the time frame required to impact treatment, as antibiotics are recommended within 1 hour of decision to treat. The company states that Genedrive MT-RNR1 ID Kit has a run time of 26 minutes. Therefore, this technology has the potential to identify those at most risk of ototoxicity from aminoglycoside antibiotics and inform treatment decisions within the time frame recommended by NICE guidance.

1.3. Interventions

This assessment will evaluate whether the Genedrive MT-RNR1 ID Kit can be used to assess the presence of the m.1555A>G variant in neonates with suspected infection or sepsis. This technology aims to identify those with the m.1555A>G gene variant. The test requires a buccal swab sample. The test is reported to take approximately 26 minutes to complete, fitting in the time frame of antibiotic prescribing within 1 hour of identification of possible infection or sepsis. There are no other tests of a similar nature that can accomplish this. The Genedrive MT-RNR1 ID kit would therefore be the first of its kind to be used as a point of care test in practice, with the possibility of informing prescribing decisions.

Such bacterial infections are a significant cause of mortality and morbidity in neonates (up to and including 28 days corrected gestational age). Expert opinion suggests the incidence of culture-confirmed neonatal infection is around 1 in 2,000 deliveries. But a larger proportion of babies will go on to receive precautionary antibiotic treatment for suspected infection. For example, approximately 30 to 60 of every 1000 blood culture samples taken in Neonatal Intensive Care Units (NICUs) 2020-2022 were positive.[3] Infection can develop into sepsis, which is the body's potentially life threatening response to an infection.

1.4. Population and relevant subgroups

The population under consideration is neonates with suspected infection or sepsis who need antibiotics (that is, a decision to start antibiotics has already been made) or who are anticipated to need antibiotics (that is, a decision to start antibiotics has not already been made).

Where data permit, the following subgroups may be considered:

- Early onset infection; occurring less than 72 hours after birth
- Late onset infection; occurring 72 hours or more after birth
- Neonates who need antibiotic treatment

- Neonates who are anticipated to need antibiotics
- Babies of different ethnicities

1.5. Place of intervention in current pathway: treatment for neonatal infections and sepsis

NICE guidance (NG195) is available on the antibiotic treatment of suspected infections and sepsis for neonates.[4] Investigations prior to starting antibiotics include a blood culture to test for bacteria in the blood, measurement of baseline C-reactive protein concentration and, if safe, performing a lumbar puncture when there is a strong clinical suspicion of early onset neonatal infection, clinical symptoms or signs suggesting meningitis. If an infection or sepsis is suspected, antibiotics must be given within 1 hour of the decision to treat with antibiotics.

For the treatment of early onset infection, intravenous benzylpenicillin with gentamicin is recommended as the first-choice antibiotic regimen. The starting dose of gentamicin should be 5mg/kg every 36 hours administered in a single dose. If a second dose of gentamicin is given, this should be 36 hours after the first dose, however, a shorter interval can be used if clinical judgement suggests this is needed. NICE guidance also recommends, in those receiving antibiotics because of risk factors for early-onset infection or clinical indicators of possible infection, to consider stopping antibiotics at 36 hours.

For babies with late onset infection who are already in a neonatal unit, a combination of narrow-spectrum antibiotics, such as intravenous flucloxacillin plus gentamicin, is recommended as first-line treatment. Local antibiotic susceptibility and resistance data should be taken into account when deciding which antibiotics to use. NICE guidance recommends considering stopping antibiotics at 48 hours for those with suspected late onset infection.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Aminoglycosides and *MT-RNR1* recommends that aminoglycoside antibiotics should be avoided in individuals with the *MT-RNR1* variant unless the high risk of permanent hearing loss is outweighed by the severity of infection and lack of safe or effective alternative therapies.[5]

Alternative antibiotic therapies may be used instead of aminoglycosides in cases of neonatal infection. However, clinical experts have advised that there are strong clinical concerns regarding antibiotic resistance to these. Alternative antibiotics include:

- Cefotaxime is a third-generation cephalosporin which may be used instead of gentamicin. It is effective against gram-negative bacteria but is less effective against gram-positive bacteria such as Staphylococcus aureus.
- Meropenem is a type of carbapenem. It is not licensed for children under 3 months of age, but its efficacy, safety and tolerability have been studied in this age group.
- Imipenem with cilastatin may be used to treat aerobic and anaerobic Gram-positive and Gram-negative infections in neonates.

The Genedrive MT-RNR1 test kit could be used before antibiotic treatment to confirm the existence of the m.1555A>G variant. During the scoping workshop, and assessment subgroup meeting, clinical experts raised the possibility that Genedrive MT-RNR1 could also be used to test mothers of neonates at risk of sepsis providing information on the likelihood of neonates inheriting the m.1555A>G variant.

This could enable informed decisions regarding antibiotic prescription, specifically whether to prescribe an alternative to aminoglycosides.

1.6. Outcomes

Four key types of outcomes will be considered (for further detail, see table 1). Firstly, intermediate measures of usage and accuracy of the equipment. Secondly, clinical outcomes concerned with mortality and morbidity (i.e., hearing loss). Thirdly, patient-reported outcomes, such as quality of life, and finally, cost-effectiveness of the intervention.

1.7. Objectives

We will summarise and critically appraise existing evidence on the clinical-effectiveness and cost-effectiveness of the Genedrive MT-RNR1 ID Kit for identifying the gene m.1555A>G variant in neonates. The following objectives are proposed:

Clinical effectiveness:

- Undertake a rapid review and, if feasible, a meta-analysis of the usability and accuracy of the Genedrive MT-RNR1 ID Kit.
- Undertake a rapid review and, if feasible, a meta-analysis of the clinical impact of the device.
- Undertake a rapid review and narratively synthesise patient and physician experience on the ease-of-use and value of use.

- Identify evidence gaps to support further evidence generation.

Cost effectiveness:

- To estimate the costs of Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates
- To conduct a rapid review of existing economic evaluations studies of the use of Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates.
- To develop an early economic model to identify key drivers, and identify evidence gaps, of the cost-effectiveness of Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates.

2. Methods for synthesising evidence of clinical effectiveness

A rapid review of the available evidence will be conducted based on Cochrane rapid review guidance.[6]

2.1. Search Strategy

The search strategy will be developed in Ovid-MEDLINE by an experienced information specialist in collaboration with the team (a sample search strategy for the clinical effectiveness review can be found in Appendix 1). The search will use the following concepts:

- Intervention: Genedrive MT-RNR1 ID test kit
- Population: m.1555A>G variant
- Standard practice: aminoglycosides
- Outcomes: ototoxicity

The search strategy will be designed using database thesaurus headings and keywords. It will be translated as appropriate to other databases.

We will limit to publications written in English language and published after 2010. Based on initial scoping, it is very unlikely that relevant studies before this date have been conducted.

Bibliographic databases:

- Ovid-MEDLINE
- Ovid-EMBASE
- CINAHL (EBSCO)

Trial registries:

- ClinicalTrials.gov
- European Clinical Trials Registry (EudraCT)
- International Standard Randomised Control Trials Number Registry (ISRCTN)

2.2. Eligibility criteria

Population

Any babies admitted to a neonatal intensive care unit (NICU) and being considered for treatment with aminoglycosides. Possible subgroups of these patients including those who present with early- (<72 hours post birth) or late-onset (>72 hours post birth) neonatal

infection; neonates who need antibiotic treatment (that is, a decision to start antibiotics has already been made); neonates who are anticipated to need antibiotics (that is, a decision to start antibiotics has not already been made); neonates of different ethnicities. Additionally, we will consider mothers tested for the variant pre-birth of the neonate.

Intervention

Genedrive MT-RNR1 ID test kit used to determine a neonate's *MT-RNR1* m.1555A>G status, when used to test:

- the neonate directly, or
- their mother (pre-birth of the neonate)

Comparator

No testing done to determine a neonate's *MT-RNR1* m.1555 variant status prior to them receiving aminoglycosides.

Outcomes

The outcomes of interest are divided into intermediate measures of the usage of the equipment and its effects on antibiotic treatment plans, clinical outcomes, patient reported outcomes, and patient experience (for further details see table 1).

Timing

Antibiotic treatment for neonates is recommended within one hour of the decision to treat. Therefore, the test is time sensitive.

Reference standard (for test accuracy data)

Laboratory based confirmatory genetic testing. Approaches may differ across genetic laboratory testing centres including techniques such as restriction enzyme assay, and sequence analysis (such as Sanger sequencing).

Study Design(s)

We will consider all study designs that provide relevant outcome data as listed in Table 1.

Setting(s)

Secondary care (hospital, neonatal unit)

Table 1. Outcomes eligible for inclusion

Outcome Type	Outcome(s) Assessed
Intermediate	• Number or proportion of neonates successfully tested • Number or proportion of mothers successfully tested • Test failure rate • Test accuracy • Impact of test result on decisions about care (for example, antibiotic use) • Impact of test implementation and use on healthcare resources (for example, time taken to do and interpret test) • Time to obtaining a sample for testing • Time to results • Time to antibiotic treatment • Number of neonates identified with m.1555A>G • Usability of the test
Clinical	• Morbidity (such as hearing loss) • Mortality
Patient-reported	• Health-related quality of life • Patient experience

2.3. Study Selection

Retrieved citations will be exported to Endnote and deduplicated before being assessed in two stages. Firstly, the citations will be exported to Rayyan, an online tool used to speed up the review process, for title and abstract screening.[7] Twenty percent of these will be screened

by two reviewers independently, with conflict resolution. One reviewer will then screen the remaining titles and abstracts. All excluded title and abstracts will then be assessed by a second reviewer, with conflicts resolved. Secondly, full text copies of these studies will be obtained and a minimum of five will be assessed by two independent reviewers. One reviewer will then assess the remaining full texts, while the second reviewer will screen the excluded full texts. Any disagreements, at either stage, will be resolved through discussion and, where necessary, a third reviewer will arbitrate.

2.4. Data extraction

A data extraction form will be designed, piloted, and finalised to facilitate standardised data extraction. Basic study information (e.g., author, year), study design, patient characteristics, recruitment method, analysis information, results, and interpretation will be extracted. One reviewer will extract the data and a second will check for accuracy. Any disagreements will be resolved through discussion and, if warranted, arbitrated by a third reviewer.

2.5. Quality assessment

Consistent with Cochrane Rapid Review guidance, we will conduct quality assessment only on key outcomes: test accuracy, test failure rate, and impact of test result on decisions about care.

We do not anticipate that any randomised controlled trials relevant to the scope have been conducted. However, if identified, we will use the latest version of the Cochrane Risk of Bias Tool to assess these trials.[8]

The risk of bias for diagnostic accuracy outcomes will be assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[9]

For all other outcomes reported in non-randomised studies, risk of bias will be assessed using the ROBINS-I tool.[10]

Quality assessment will be completed by one reviewer and independently checked by a second reviewer. Any disagreements will be resolved through discussion and, where necessary, consultation with a third reviewer.

2.6. Method of analysis/synthesis

We will present the results of the data extraction in structured tables and an accompanying narrative summary. Where there are sufficient data, they will be pooled using appropriate

meta-analytic techniques, as outlined below. However, it is anticipated that a narrative synthesis will be required for most outcomes.

2.6.1. Synthesis of intermediate outcomes

Most outcome data are expected to be narratively synthesised, with an accompanying table used to give an overview of the outcomes of interest. Where sufficient diagnostic test accuracy data (e.g. 2×2 contingency tables) are available, they will be pooled using the bivariate meta-analysis of sensitivity and specificity.[11]

2.6.2. Synthesis of clinical and patient-reported outcomes

Available quantitative data on mortality and morbidity (including patient-reported outcomes) will be tabulated or plotted. Where there are sufficient data, we will conduct random-effects meta-analysis. If not, narrative synthesis will be performed. This will be accomplished by comparing tabulated results across studies to identify broad evidence of effectiveness.

Health-related quality of life data will be based on descriptive data elicited from UK patients using the EQ-5D and valued using UK general population preferences where possible.

2.6.3. Synthesis of patient experience data

Any quantitative data on patient experience will be synthesised narratively or meta-analysed as described for clinical and patient-reported outcomes above.

Qualitative data will be analysed using thematic synthesis to identify recurring and emergent themes and will be presented in a narrative synthesis.

3. Methods for synthesising evidence of cost-effectiveness

The economic evaluation will assess the cost-effectiveness of Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates compared to current clinical standard (no testing). The decision problem for the economic evaluation is summarised in Table 2.

Table 2: Decision problem addressed by the economic evaluation

Item	Description
Populations	Neonates who need antibiotic treatment or who are anticipated to need antibiotic treatment, and who are being considered for treatment with aminoglycosides
Intervention	Genedrive MT-RNR1 ID Kit used to test for single nucleotide polymorphism m.1555A>G variant status, when used to test: • the neonate directly, or • their mother (pre-birth of the neonate)
Comparators	No point of care testing for single nucleotide polymorphism m.1555A>G prior to them receiving aminoglycosides
Perspective	NHS England and personal social services
Time horizon	Lifetime
Outcomes	1. Cost per Genedrive system test 2. Incremental cost per hearing loss case prevented 3. Incremental cost per QALY gained

The decision population consists of neonates in need of antibiotic treatment (both early-onset and late-onset infection) and who are being considered for treatment with aminoglycosides.

The economic assessment will be undertaken from the perspective of the NHS and Personal Social Services. The time horizon for economic evaluation will be long enough (e.g., patient lifetime) to capture all related cost and outcomes of using the Genedrive test for detecting single nucleotide polymorphism m.1555A>G.

Costs of Genedrive testing, investigations and ongoing care for hearing loss, treatment associated with antibiotics (including monitoring during use) will be included in the analysis. These data will be used to estimate the cost per Genedrive system test and the incremental cost per hearing loss case prevented. A focused literature review will be conducted to identify evidence on health-related quality of life (HRQol) associated with hearing loss. If adequate HRQoL data are identified, then the incremental cost per QALY gained will be estimated. Both costs and benefits will be discounted at 3.5% per annum.

The main economic questions to be addressed are:

1) What are costs, from a UK NHS and Personal Social Services perspective, of Genedrive MT-RNR1 ID Kit, for detecting single nucleotide polymorphism m.1555A>G in neonates?
2) What existing, published cost-effectiveness studies are available about Genedrive MT-RNR1 ID Kit, for detecting single nucleotide polymorphism m.1555A>G in neonates?
3) What are the key drivers of the cost and effectiveness of Genedrive MT-RNR1 ID Kit roll-out for detecting single nucleotide polymorphism m.1555A>G in neonates.

3.1. Rapid review of cost-effectiveness studies:

The External Assessment Group (EAG) will conduct a rapid review to identify existing economic evaluations of Genedrive MT-RNR1 ID Kit for detecting single nucleotide

polymorphism m.1555A>G in neonates. All evidence will be evaluated according to the recommendations of the NICE health technology evaluations manual .[12]

A search filter to include full economic evaluations (e.g., cost-minimisation, cost-effectiveness, cost-consequence, cost-utility, and cost-benefit analyses) assessing both the costs and consequences of the test will be applied to the search strategies and the electronic databases. The search strategies will combine terms capturing the interventions (using Genedrive system) or current clinical pathway and the target population (neonates). The EAG will apply search terms to identify full economic evaluation study designs.

In addition, the EAG will contact clinical experts in the field for details of published and unpublished studies (grey literature) which they may be aware of. Furthermore, included SRs and company submissions will be searched for additional references.

After finalising the search strategy, the following databases will be searched to find relevant studies:

- Ovid MEDLINE
- Embase
- Cochrane databases of systematic reviews (CDSR) (Cochrane)
- Cochrane Central Database of Controlled Trials (CENTRAL) (Cochrane)
- Research Papers in Economics (RePEc)

Standardised forms will be used by the EAG to conduct data extraction from included studies. The data will be extracted by one reviewer for each study and then checked by a second reviewer. Specifically, information will be extracted on the interventions and comparators, study population and setting, main analytic approaches (e.g. patient-level data analysis/ decision-analytic modelling), primary/secondary outcome specified for the economic analysis, details of adjustment (e.g., mapping) for quality of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).The EAG will also use the consolidated health economic evaluation reporting standards (CHEERS) checklist to quality assess the economic evaluation methodology.[13]

The data included in the rapid review will be synthesised narratively for both costs and effectiveness items. We will provide the results in terms of tables and figures, if possible and will also consider the implication of the included studies characteristics and its implication for the scope of this study (PICO) identified by the NICE scope.

3.2. Development of an early health economic model

Following completion of the rapid review of economic evaluations, the EAG will develop an early economic model incorporating the pathways of care that individuals follow under standard practice in the UK NHS. The model will address the decision problem set out in Table 2 and the model structure will map out use of the Genedrive system to detect nucleotide polymorphism m.1555A>G.

The aim of an early economic model is to identify key drivers of costs and effectiveness of the Genedrive system roll-out to detect nucleotide polymorphism m.1555A>G. Outcomes will include lifetime impact on costs for the NHS and personal social services (PSS) of aminoglycoside-induced hearing-loss in neonates and, if data are available, we will also

identify lifetime impact on quality adjusted life years (QALYs) of aminoglycoside-induced hearing-loss in neonates (potentially also for family members/carers as well).

The economic model will be developed according to standard modelling guidelines.[14,15] The face validity of the model will be checked by clinical and patient experts. The model structure will also be reviewed by our clinical and methodological experts for appropriateness to the current NHS clinical and diagnostic pathways.

The model will incorporate the risk of ototoxicity/hearing loss for people with and without *MT-RNR1* gene m.1555A>G variant who have (1) aminoglycoside and (2) non-aminoglycoside alternative; the likely prevalence of *MT-RNR1* gene m.1555A>G variant in neonates (and how does this vary across different groups); and diagnostic failure as well as diagnostic accuracy. The time to antibiotic delivery using the Genedrive system will be explored within the model and where data are not available from the literature we will incorporate clinical expert opinion.

We will include cost data relating to the Genedrive system (Genedrive MT-RNR1 ID kit to detect m.1555A>G variant and Genedrive system software), the medical management of people with suspected/diagnosed hearing loss including hearing tests (automated otoacoustic emissions (AOAE), auditory brainstem response (ABR)), and the need for Cochlear implants. To identify cost and resource use evidence, the EAG will also search the same sources identified for the economic evidence supplied by the test manufacturers together with NHS reference costs,[16] the unit costs of health and social care (Personal Social Services Research Unit [PSSRU]),[17] and the British National Formulary (BNF).[18] All costs will be updated to price year 2021/22.

HRQoL data, where available, will be extracted from included cost-effectiveness studies and supplemented with any patient reported outcome data relating to quality of life from the rapid review of diagnostic test evaluations. In addition, a targeted literature search will also be conducted specifically for publications reporting HRQoL or health state utilities for the populations of interest.

4. Handling the company submission

All data submitted by the company or other stakeholders will be considered by the EAG if received by 2nd December, 2022. Data received after this date will be considered if practicable and at the discretion of the EAG.

If these data meet the eligibility criteria set out in the protocol, they will be extracted, and quality assessed in the rapid review. Any 'commercial in confidence' data provided by the company, and specified as such, will be highlighted in blue and underlined in the report. Any 'academic in confidence' data provided by the company, and specified as such, will be highlighted in yellow and underlined in the report.

Confidential data will be stored securely and will only be accessible to members of the project team.

5. Competing interests of authors

None of the authors have any conflicts of interest.

6. Timetable and milestones

Milestone	Date to be completed
Submission of final protocol	22nd September 2022
Submission of progress report	25th October 2022
Submission of draft report	18th November 2022
Submission of final report	16th December 2022

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Appendix 1

Sample search strategy for the clinical effectiveness review designed in Ovid-MEDLINE

#	Searches	
1	Point-of-Care Systems/	
2	(POCT or "point of care" or "point-of-care").ti,ab,kw.	
3	genedrive.ti,ab,kw.	
4	PALoH.ti,ab,kw.	
5	(pharmacogenetics or pharmacogenomics or "genetic testing" or genotyp* or pyrosequencing or sequencing).ti,ab,kw.	
6	or/1-5	
7	"mt.1555A>G".ti,ab,kw.	
8	"1555A>G".ti,ab,kw.	
9	A1555G.ti,ab,kw.	
10	"1555 A to G".ti,ab,kw.	
11	((penetrance or snp or polymorphism or mutation) adj3 "1555").ti,ab,kw.	
12	or/7-11	
13	exp Aminoglycosides/	
14	Gentamicin.ti,ab,kw.	
15	aminoglycoside*.ti,ab,kw.	
16	(anti?biotic* or anti?bacterial*).ti,ab,kw.	
17	exp Anti-Bacterial Agents/ae, to [Adverse Effects, Toxicity]	
18	or/13-17	
19	induc*.ti,ab,kw.	
20	ototoxicity.ti,ab,kw.	
21	exp Hearing Loss/	
22	Ototoxicity/	
23	Deaf*.ti,ab,kw.	
24	"hearing loss".ti,ab,kw.	
25	or/19-24	
26	6 and 12 and 18 and 25	
27	"Genedrive MT-RNR1 ID".ti,ab,kw.	
28	26 or 27	