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Newborn screening for galactosaemia (Review)

Lak R, Yazdizadeh B, Davari M, Nouhi M, Kelishadi R

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TABLE OF CONTENTS

[Intervention Review]

Newborn screening for galactosaemia

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ABSTRACT

Background

Classical galactosaemia is an autosomal recessive inborn error of metabolism caused by a deficiency of the enzyme galactose-1-phosphate uridyltransferase. This is a rare and potentially lethal condition that classically presents in the first week of life once milk feeds have commenced. Affected babies may present with any or all of the following: cataracts; fulminant liver failure; prolonged jaundice; or *Escherichia coli* sepsis. Once the diagnosis is suspected, feeds containing galactose must be stopped immediately and replaced with a soya-based formula. The majority of babies will recover, however a number will not survive. There are long-term complications of galactosaemia, despite treatment, including learning disabilities and female infertility. It has been postulated that galactosaemia could be detected on newborn screening and this would prevent the immediate severe liver dysfunction and sepsis.

Objectives

To assess whether there is evidence that newborn screening for galactosaemia prevents or reduces mortality and morbidity and improves clinical outcomes in affected neonates and the quality of life in older children.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from electronic database searches, handsearches of relevant journals and conference abstract books. We also searched online trials registries and the reference lists of relevant articles and reviews.

Date of the most recent search of Cochrane Cystic Fibrosis Group's Trials Register: 18 December 2017.

Date of the most recent search of additional resources: 11 October 2017.

Selection criteria

Randomised controlled studies and controlled clinical studies, published or unpublished comparing the use of any newborn screening test to diagnose infants with galactosaemia and presenting a comparison between a screened population versus a non-screened population.

Data collection and analysis

No studies of newborn screening for galactosaemia were found.

Main results

No studies were identified for inclusion in the review.

Authors' conclusions

We were unable to identify any eligible studies for inclusion in this review and hence it is not possible to draw any conclusions based on randomised controlled studies. However, we are aware of uncontrolled studies which support the efficacy of newborn screening for galactosaemia. There are a number of reviews and economic analyses of non-trial literature suggesting that screening is appropriate.

PLAIN LANGUAGE SUMMARY

Screening newborn babies for galactosaemia

Review question

We reviewed the evidence for screening newborn babies for galactosaemia in order to prevent or reduce death and illness, to improve clinical outcomes in affected babies and to improve the quality of life in affected older children.

Background

Galactosaemia is an inherited disease that affects the body's ability to breakdown the milk sugar galactose. Newborn babies with galactosaemia can have a variety of symptoms in the first weeks of life including poor feeding, cataracts, jaundice, an enlarged liver with liver failure or severe infection. Without treatment, babies with galactosaemia are often very unwell and highly likely to die from liver failure. Unfortunately, despite treatment, long-term complications for people with galactosaemia include learning difficulties and fertility problems (in females).

Search date

The evidence is current to: 11 October 2017.

Study characteristics

No studies were identified for inclusion in the review.

Key results

No suitable studies were found, but we are aware of some uncontrolled studies which suggest newborn screening for galactosaemia and early treatment can reduce death and illness. Future research is needed to provide robust evidence for or against screening.

Quality of the evidence

We have not identified any relevant studies for inclusion in this review.

BACKGROUND

Please see the glossary for an explanation of terms (Appendix 1).

Description of the condition

Galactosaemia is an autosomal recessive disorder of galactose metabolism. It occurs as a consequence of a deficiency of one of three principal enzymes involved in the metabolism of galactose. These enzymes are galactokinase (GALK), galactose-1-phosphate uridyltransferase (GALT) and uridine-diphosphate galactose-4' epimerase (GALE). The most common deficiency is that of the transferase enzyme, which causes 'classical galactosaemia' (Handerson 2002). Affected infants are born healthy, but experience a rapid, and often, devastating decline following exposure to

the galactose found in breast milk or milk formula. Acute symptoms can progress in a matter of days ranging from jaundice, vomiting, and diarrhoea to failure to thrive, hepatomegaly, fulminant liver failure and *Escherichia coli* (*E coli*) sepsis. Without treatment, affected infants often die in the neonatal period (Fridovich-Keil 2008). Females with galactosaemia are at an increased risk of premature ovarian failure and the majority of affected individuals do have some long-term complications.

The global frequency of galactosaemia is estimated at approximately one in every 62,000 live births; in the USA a recent prevalence of one in 30,000 to one in 60,000 live births has been reported (Pyhtila 2015). Across Europe, the incidence varies greatly (Morel-Garcia 2014), with a much lower frequency reported in Asian populations (Choi 2014). The Irish Traveller population has a very high incidence of 1 in 480 births (Murphy 1999).

Description of the intervention

Newborn screening for galactosaemia was designed to detect both classical galactosaemia as well as variant forms (e.g. Duarte galactosaemia) as screening largely fulfilled the Wilson Jungner criteria (see glossary) (Pamela 2007). A number of biochemical methods have been used to screen for galactosaemia, the most common being the measurement of galactose and galactose-1-phosphate (G-1-P) in blood spots (Ohlsson 2011). Galactosaemia is generally screened for in those parts of the world with a high prevalence or an expansive screening programme, or both . In countries where newborn screening is not standard practice, cases can only be detected once the affected individuals present with clinical symptoms.

How the intervention might work

Newborn screening, if performed in the first few days of life, provides an opportunity for a diagnosis either before or just as the infant presents with symptoms. Early diagnosis allows a change to a soya-based formula and thus reduces the risk of liver failure and its complications and *E coli* sepsis. In a 10-year period, mortality was reportedly reduced more than 10-fold in children with galactosaemia as a result of newborn screening (Padilla 2008). Unfortunately though, newborn screening does not prevent the longer-term complications of learning disability and ovarian failure as these are due to the endogenous production of galactose. Thus, the importance of newborn screening lies in preventing the initial liver failure and sepsis. Currently, most infants with galactosaemia are hospitalised in neonatal intensive care units, with newborn screening expected to reduce the cost per stay by USD 12,000 per child (Padilla 2008).

Why it is important to do this review

As early as 1978, advocates of newborn screening stated that "Galactosemia screening should be routine for all newborn infants. It is a disorder with definite and severe complications, but one in which the complications can be prevented with simple and inexpensive treatment" (Botlin 2005; Levy 1978). Many rare diseases do not fully fulfil the Wilson Jungner criteria, but galactosaemia is certainly a treatable disorder and early detection can reduce early morbidity and mortality. Robust evidence is required to support the institution of galactosaemia newborn screening programs in those countries where it is not currently undertaken.

OBJECTIVES

To determine whether newborn screening for classical galactosaemia prevents or reduces mortality and morbidity and improves clinical outcomes in affected neonates and the quality of life in older children.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi- randomised controlled trials (quasi-RCT) where participants are prospectively allocated to either screening via a blood test (e.g. from the heel prick) or no screening. No language restrictions will be placed on studies considered for inclusion in this review, and published or unpublished sources will be considered.

Types of participants

All newborn populations eligible for inclusion in a screening study in the first week of life.

Types of interventions

We will compare the population screened for classical galactosaemia versus the non-screened population i.e. no intervention. Screening by blood test (heel prick or venous blood specimen) undertaken in the first week of life using any biochemical test such as the Beutler test (also known as the fluorescent spot test), calorimetric test, fluorescent galactose oxidase method, Guthrie's method, etc to measure total galactose or GAL-1-P, etc. Other diagnostic methods, such as urine and genetic testing will be excluded.

Types of outcome measures

Primary outcomes

1. Mortality (galactosaemia-related)
2. Morbidity (in the neonatal period)
   i) liver failure
   ii) sepsis

Secondary outcomes

1. Quality of life as measured by a validated scoring system such as SF-6D questionnaire derived from the SF-36 form (Ware 1992) (see glossary Appendix 1)
2. Clinical outcomes
   i) organ dysfunction or failure, e.g. liver, kidney, eye, ovarian, etc measured by biochemical tests (for liver function, kidney function and for eye), physical examination and sonography (ovarian failure)
   ii) developmental problems
   iii) speech difficulties
   iv) learning difficulties
   v) mental retardation assessed by standardised developmental or IQ tests and also Ages and Stages Questionnaire (ASQ) (Squires 1997)
3. Reduction in galactose-1-phosphate levels

Search methods for identification of studies

We used a combination of electronic and handsearches for this review. We did not restrict the searches by language, year or publication status.

Electronic searches

We searched the Group's Inborn Errors of Metabolism Trials Register to identify relevant studies using the term: galactosaemia.
The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), weekly searches of MEDLINE and the prospective handsearching of one journal - *Journal of Inherited Metabolic Disease*. Unpublished work is identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cystic Fibrosis and Genetic Disorders Group website.
Date of the most recent search: 18 December 2017.
We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 9) in the Cochrane Library (searched 11 October 2017);
- PubMed (www.ncbi.nlm.nih.gov/pubmed; 1946 to 11 October 2017);

We also searched the following trials registries and other resources:

- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; searched 11 October 2017);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; searched 11 October 2017);
- Grey Literature Report (www.greylit.org; searched 11 October 2017);
- System for Information on Grey Literature in Europe (www.opengrey.eu ; searched 11 October 2017);

For details of our search strategies, please see Appendix 2.

Searching other resources

· We would have checked the bibliographies of any included studies and any relevant systematic reviews identified for further references to relevant trials had we found any. We hand searched the Journal of Inherited Metabolic Disease and the Galactosemia Foundation Bi-Annual International Conference, details in Appendix 3.

Data collection and analysis

The review authors planned to follow the recommended strategies for data collection and analysis as documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Selection of studies

Two review authors (RL and MNJ) independently scanned the titles and abstracts to determine the studies to be further assessed. They examined all potentially relevant articles, as full text if available. If there had been any differences in opinion, the authors had planned to resolve these by discussion with a third author. If it had not been possible to resolve the disagreement, they would have listed the article as 'Awaiting classification' and contacted the study authors for clarification.

Data extraction and management

To date, we have not identified any studies for inclusion in the review, but if we are able to include any studies in future, we plan to employ the following methods.
Two authors (RL and MNJ) will independently extract data from eligible studies using a standard data extraction form customised for this review. The authors plan to pilot test the data extraction

form before using it in the review and will modify it accordingly if needed. They will record information about study and participant characteristics, the intervention and the outcomes. If there are any uncertainties, they will contact the primary investigators of the study in question for clarification. They will check the data for accuracy and consistency, and resolve any disagreements by consensus or by consulting a third author.
The authors will record details of all participants with any type of galactosaemia and their genotypes.

Assessment of risk of bias in included studies

According to the method described in the *Cochrane Handbook for Systematic Reviews of Interventions*, two authors will independently assess the risk of bias (Higgins 2011b). They will resolve possible disagreements by consensus, or by consulting of a third author. They will assess the following criteria:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias); and
- other bias.

Measures of treatment effect

For dichotomous outcomes (e.g. mortality) the authors will express the measure of effect as a risk ratio (RR) with 95% confidence intervals (CIs); and for continuous outcomes (e.g. quality of life, biochemical tests, growth charts, IQ tests and ASQ), they will express the measure of effect as a mean difference (MD) with 95% CIs. If outcomes are reported using different scales, e.g. quality of life, we will use standardised mean difference (SMD) and corresponding 95% CIs.

Unit of analysis issues

Cluster-randomised studies and studies of cross-over design are not appropriate for this review.

Dealing with missing data

The authors plan to obtain any relevant missing data by contacting the primary investigators.

Assessment of heterogeneity

The authors plan to assess any identified heterogeneity between studies using the I^2 statistic (Higgins 2003). The values of I^2 lie between 0% and 100%, and a simplified categorisation of heterogeneity that they plan to use is:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If there is a sufficient number of included studies in the review (at least 10), the authors will assess reporting bias and small study effects using funnel plots. The authors will identify and report on any selective reporting in the included studies.

Data synthesis

The authors plan to use a fixed-effect model if they are able to enter data in a meta-analysis using Cochrane's Review Manager software (Review Manager 2014). If they find statistical heterogeneity between studies (either moderate, substantial or considerable heterogeneity, as defined above), the authors will use a random-effects model.

Subgroup analysis and investigation of heterogeneity

If the authors identify a high degree of heterogeneity between any included studies, they will carry out subgroup analyses as reported below.

- Comparison of those screened at different time points (day 1 of life versus day 2 of life versus day 3 etc) since the age at screening is an important factor.
- Comparison of galactose-1-phosphate levels to assess how these affect developmental outcomes (comparing those who maintain higher levels throughout childhood to those who do not).
- Comparison of those children with a family history of galactosaemia treated with soya formula from birth to those children not treated in this way with regards to clinical outcomes listed above.

Sensitivity analysis

The authors plan to perform sensitivity analyses to investigate the impact of a high risk of bias for generation of randomisation sequence and allocation concealment on the robustness of the results of the included studies. They also plan to perform sensitivity analyses to assess the overall risk of bias by outcome.

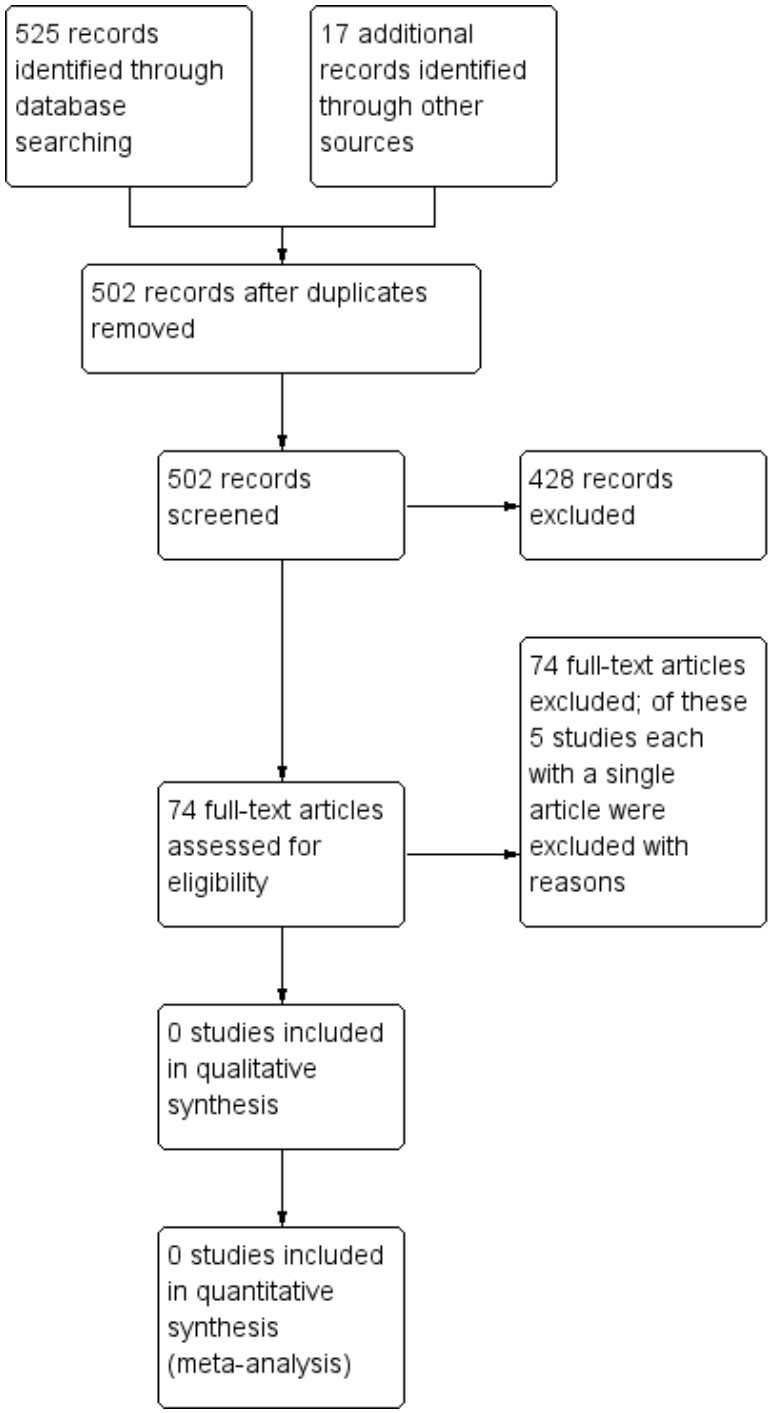
RESULTS

Description of studies

Results of the search

A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified five studies which were potentially eligible for inclusion in the review. However, on closer inspection, all of these studies were excluded (see below for reasons). We did not identify any other studies in our additional searches.(see Figure 1)

Figure 1. Study flow diagram.



Included studies

No studies were included in the review.

Excluded studies

Five studies were excluded (see Characteristics of excluded studies). One of the excluded studies examined the effectiveness of a particular test for screening and was not a study comparing newborn screening to no screening. The remaining four studies assessed different treatments for galactosaemia and not newborn screening.

Risk of bias in included studies

No studies were found that were eligible for inclusion in the review.

Effects of interventions

No studies were identified for inclusion in the review.

DISCUSSION

Summary of main results

There were no completed or ongoing RCTs that were relevant to this review and there are no results to summarise.

Overall completeness and applicability of evidence

This review did not identify any completed RCTs and therefore there is no evidence that can be assessed.

Quality of the evidence

No RCTs of screening were found for inclusion in this review and there is no evidence that can be assessed.

Potential biases in the review process

We conducted a comprehensive search, searching data sources including multiple databases, and clinical trial registries to ensure that all relevant RCTs would be captured. Two authors independently assessed all of the review processes.

Agreements and disagreements with other studies or reviews

Due to the absence of evidence from RCTs, we were unable to compare our results with other published articles. Our search, only identified a small body of mid-level evidence derived from observational studies such as cohort, case-control and cross-sectional studies, mainly reporting incidence or prevalence, with the bulk of the evidence being low level, derived from retrospective studies, case reports and expert opinion articles.

Currently, there are no adequate comparative studies to determine the effectiveness of neonatal screening for galactosaemia compared to the implementation of other measures designed to prevent severe, acute complications (e.g. protocol alerts, surveillance programmes, opportunistic screening). The only comparative data come from the UK paediatric surveillance programme, which points to similar incidences of severe cases and mortality in the regions which have and have not implemented galactosaemia screening programmes, but does not take into account the characteristics of public healthcare planning in the UK (Honeyman 1993). A recent systematic review concluded that based on the indirect assumptions and descriptive data presented by both the Swedish and German screening programs, one could assume that screening might reduce the risk of mortality and illness in babies if screening results are obtained before the 7th to 8th day of life (Varela Lema 2014). This should be confirmed in properly designed studies.

AUTHORS' CONCLUSIONS

Implications for practice

No studies were found for inclusion in the review. Galactosaemia is a potentially fatal disease and given the known clinical course of classical galactosaemia, newborn screening could prevent significant morbidity and mortality although there is no direct evidence to support this. We agree with the recommendation by Levy in the paper, "Galactosemia screening should be routine for all newborn infants. It is a disorder with definite and severe complications, but one in which the complications can be prevented with simple and inexpensive treatment" (Levy 1978).

Implications for research

No controlled studies of the effectiveness of newborn screening for galactosaemia appear to have been undertaken. If the implementation of a national galactosaemia programme were to be considered, it would be important to reach a consensus on the screen-

ing protocol to be used, based on scientific evidence and expert opinion.

ACKNOWLEDGEMENTS

We thank the referees and editors of the Cystic Fibrosis and Genetic Disorders Group for their comments and valuable assistance.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Crabbe 1985	A study of treatment for cataracts in diabetes and galactosaemia; not a newborn screening study
Knerr 2014	Study of the effects of temporary low-dose galactose supplements in children of over 5 years with classical galactosaemia; not a newborn screening study
Manis 1997	A study of treatment with oral uridine and cognitive functioning in people with classical galactosaemia; not a newborn screening study
Panis 2006	A study of the effect of calcium, vitamins K1 and D3 on bone in galactosaemia; not a newborn screening study
Schon 1976	A study of rapid fluorescence test (Weidemann) as mass screening procedure for galactosaemia in newborn infants in regard to sensitivity and specificity to a screening test; not relevant to our objectives

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Glossary

Term	Explanation
Ages and Stages Questionnaire (ASQ)	A parent-completed child monitoring system (previously called the Infant/Child Monitoring Questionnaires) developed in 1980 as an alternative screening assessment for infants and young children and revised in 1997 (Squires 1997).
ataxia	A neurological sign consisting of lack of voluntary coordination of muscle movements that includes gait abnormality. Ataxia is a non-specific clinical manifestation implying dysfunction of the parts of the nervous system that coordinate movement, such as the cerebellum
endogenous	Growing or originating from within an organism, tissue or cell
fulminant liver disease	The rapid development of liver injury, usually due to viruses or toxins that overwhelm the liver, leading to liver cells being injured and dying. These liver cells are replaced by scar tissue instead of normal liver cells; this continues until there are not enough liver cells to do their job
galactose	A component part of the sugar lactose commonly found in dairy product
hepatomegaly	Having an enlarged liver.
SF-36	A 36-item short-form which was constructed to survey health status in the Medical Outcomes Study and is designed for use in clinical practice and research, health policy evaluations, and general population surveys. It includes one multi-item scale that assesses eight health concepts: 1. limitations in physical activities because of health problems; 2. limitations in social activities because of physical or emotional problems; 3. limitations in usual role activities because of physical health problems; 4. bodily pain; 5. general mental health (psychological distress and well-being); 6. limitations in usual role activities because of emotional problems; 7. vitality (energy and fatigue); and 8. general health perceptions.
Wilson Jungner criteria	A set of criteria proposed in the 1960s by James MG Wilson and Gunnar Jungner for assessing the validity of screening for a given condition 1. The condition should be an important health problem.

(*Continued*)

	2. There should be a treatment for the condition. 3. Facilities for diagnosis and treatment should be available. 4. There should be a latent stage of the disease. 5. There should be a test or examination for the condition. 6. The test should be acceptable to the population. 7. The natural history of the disease should be adequately understood. 8. There should be an agreed policy on whom to treat. 9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole. 10. Case-finding should be a continuous process, not just a "once and for all" project.

Appendix 2. Electronic searches

Database or resource	Date last searched	Strategy
Cochrane Central Register of Controlled Trials (CENTRAL)	11 October 2017	#1 MeSH descriptor: [Galactosemias] #2 MeSH descriptor: [Neonatal Screening] #3 MeSH descriptor: [Mass Screening] explode all trees #4 (newborn or neonatal or mass or universal or communit*) near/3 screen* #5 (galactose or galactose 1- phosphate or Galactose-1-phosphate uridyl transferase or Galactose-1-phosphate uridyl transferase deficiency or galactosemia* or galactosaemia*) #6 #1 or #5 #7 #2 or #3 or #4 #8 #6 and #7
PubMed (1946 onwards)	11 October 2017	#1 randomized controlled trial [pt] #2 controlled clinical trial [pt] #3 randomized [tiab] #4 placebo [tiab] #5 drug therapy [sh] #6 randomly [tiab] #7 trial [tiab] #8 groups [tiab] #9 #1 OR #2 OR # 3 OR #4 OR #5 OR #6 OR #7 OR #8 #10 (animals [mh] NOT humans [mh]) #11 #9 NOT #10 #12 "Galactosemias"[Mesh:NoExp] #13 "Neonatal Screening"[Mesh:NoExp] #14 Mass Screening"[Mesh] #15 (newborn OR neonatal OR mass OR universal OR communit*) AND screen* #16 galactose OR galactose 1- phosphate OR Galactose-1-phosphate uridyl transferase OR Galactose-1-phosphate uridyl trans-

(*Continued*)

		ferase deficiency OR galactosemia* OR galactosaemia* #17 #12 OR #16 #18 #13 OR #14 OR #15 #19 #11 AND #17 AND #18 *Lines #1 - #11 are the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format*
Clinicaltrials.gov	11 October 2017	galactosemia OR galactosaemia
WHO ICTRP	11 October 2017	galactosemia OR galactosaemia
Graylit.org	11 October 2017	galactosemia OR galactosaemia
Opengray.eu	11 October 2017	galactosemia OR galactosaemia

Appendix 3. Handsearching

Journal or conference	**Strategy**
Journal of Inherited Metabolic Disease 13 November 1978 (Issue 1) to 01 January 2017 (Issue 1)	galactosemia OR galactosaemia
Galactosemia Foundation Bi-Annual International Conference in the USA 2010 in Bloomington, Minnesota 2012 in Dallas, Texas 2014 in Orlando, Florida	galactosemia OR galactosaemia

Initiallly searched for the date range 13 November 1978 to 04 August 2016 and search updated 01 January 2017.

CONTRIBUTIONS OF AUTHORS

Rohollah Lak (RL): draft protocol, develop search strategy, study selection, data extraction, data entry, data analysis, data interpretation, draft review and update future review versions.

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Rohollah Lak acts as guarantor for this review.

DECLARATIONS OF INTEREST

All the authors of this Cochrane Review declare that there are no conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There was a post hoc change to the outcome measures to clarify the focus of the review to primarily assess the effect of newborn screening on neonates.

INDEX TERMS

Medical Subject Headings (MeSH)

*Neonatal Screening; Galactosemias [*diagnosis]

MeSH check words

Humans; Infant, Newborn