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Statins for Smith-Lemli-Opitz syndrome

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Current and planned contributions

- Conceiving the review: RB
- Designing the review: RB
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- Providing a clinical perspective: RB, SB, AR, FP
- Providing a policy perspective: RB, AR, FP
- Writing the protocol: RB, YF
- Performing previous work that was the foundation of the current review: SB, FP

DECLARATIONS OF INTEREST

Rami A. Ballout, Alan T. Remaley, Yi-Ping Fu, and Alicia Livinski have no known conflicts of interest to be disclosed.

Simona Bianconi and Forbes D. Porter conducted and published the largest trial to date on statin therapy in SLOS patients: “A Placebo-Controlled Trial of Simvastatin Therapy in Smith-Lemli-Opitz Syndrome” (Wassif 2017). As a result, they will be excluded from evaluating the eligibility of that study for inclusion in our review, as well as their exclusion from any subsequent data handling pertaining to that study.

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Abstract

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

1. To evaluate the efficacy of statin therapy in reducing the frequency or severity of the neurobehavioral abnormalities seen in people with SLOS (e.g. aggression, anxiety, irritability, self-mutilation, autistic behaviors, sleep disturbances, etc.) (Wassif 2017).

2. To evaluate the potential effects of statin therapy on survival.

BACKGROUND

Description of the condition

Smith-Lemli-Opitz syndrome (SLOS; OMIM 270400) is an ultrarare autosomal recessive metabolic disorder arising from a defect in 7-dehydrocholesterol reductase (DHCR7), the enzyme catalyzing the final step of the cholesterol biosynthesis pathway. This results in a deficiency of endogenous cholesterol and the accumulation of several of its early upstream precursors, most notably 7-dehydrocholesterol (7DHC) and 8-dehydrocholesterol (8DHC). Clinically, SLOS manifests with multiple congenital malformations and a spectrum of neurobehavioral and cognitive abnormalities. It is mainly the resultant cholesterol deficiency, and possibly the accumulation of 7DHC, which interfere with normal fetal development in SLOS, particularly of the central nervous system, leading to the various neurobehavioral and cognitive manifestations characteristic of the disorder in the postnatal period (Kelley 2000; Nowaczyk 1999; Porter 2008).

Classically, SLOS is characterized by pre- and post-natal growth retardation, microcephaly, multiple malformations such as cleft palate, hypospadias, gingival abnormalities, or ambiguous genitalia (especially in males), photosensitivity, polyneuropathy, and characteristic facial dysmorphic features such as bitemporal narrowing, ptosis, shortened nose with anteverted nares, or micrognathia (Kelley 2000; Nowaczyk 2012a; Nowaczyk 2013). SLOS is also associated with various limb anomalies, most importantly a Y-shaped 2,3-toe syndactyly that is regarded pathognominic to the condition, short limbs, or post-axial polydactyly with shortened and posteriorly displaced thumbs. In addition, some individuals with SLOS may present with severe organ malformations, particularly affecting the brain, such as ventriculomegaly, corpus callosum thinning, holoprosencephaly, or myelination defects (or any combination of these). Several other multisystem organ malformations can also be seen, including kidney cysts, pyloric stenosis, Hirschsprung disease, cholestatic liver disease, congenital cataracts, optic atrophy, total anomalous pulmonary venous return, and severe cardiac malformations (most commonly atrioventricular canal defects) (Kelley 2000; Nowaczyk 2013).

The classical cognitive and neurobehavioral manifestations of the disorder include intellectual disability of various degrees, sensory hyperreactivity and irritability particularly during infancy, sleep disturbances, anxiety, hyperactivity, emotional lability, self-mutilation, motor mannerisms, social and communication deficits, and autism spectrum disorders (ASD) usually in childhood (Kelley 2000; Nowaczyk 2013; Tierney 2001). The overall incidence of SLOS, including its mild and severe variants, is around 1 in 20,000 to 40,000 births, with regional differences in these rates owing possibly to founder effects (Cross 2015; Nowaczyk 2013). The overall life span of individuals with SLOS is generally shortened, with premature death often arising from underlying severe malformations. However, based on our clinical experience, the gastrointestinal abnormalities commonly encountered in SLOS, mainly delayed gastric emptying, poor feeding, anorexia, and the inability to digest enteral nutrients (often termed 'feeding disorder') (Kelley 2000; Nowaczyk 2012b), are often the leading cause of death in infants due to malnutrition and subsequent sepsis following the initiation of parenteral nutrition or gastrostomy tube placement. In addition, children with SLOS have been reported to die from sudden and overwhelming infections, despite their lack of an identifiable underlying immune defect (Kelley 2000). Moreover, because cholesterol is a precursor of many steroid hormones of endocrine function as well as others that are upregulated during physiological stress states (e.g. infection), individuals with SLOS sometimes die from sudden episodes of hypoglycemia or adrenal insufficiency-like state following infection, trauma, prolonged decrease in oral intake, or surgery (Bianconi 2011; Chemaitilly 2003; Jayamanne 2018). Nonetheless, formal studies investigating the precise causes of death in SLOS are still lacking (Kelley 2000).

Description of the intervention

There is currently no consensus on an 'optimal' standard therapy for individuals with SLOS, partly because of the rare and therefore poorly studied nature of the condition. However, based on our understanding of the underlying biochemistry and purely empirical data, cholesterol supplementation has long been regarded as the mainstay of treatment, despite its limited benefits. This is primarily due to the inability of cholesterol to cross the blood-brain barrier (BBB), and its limited intestinal absorption when orally supplemented in the diet (Elias 1997; Nowaczyk 1999; Porter 2008; Riley 2011; Svoboda 2012). Nonetheless, several studies in children with SLOS receiving cholesterol supplementation have demonstrated improved physical growth (Irons 1997; Nwokoro 1997), gastrointestinal symptoms and infection tolerance (Elias 1997), and nerve function (Starck 2002a). Cholesterol supplementation has also been shown to reduce the UV-A photosensitivity classically seen in individuals with SLOS (Azurdia 2001). However, it failed to show benefit in alleviating the neurobehavioral manifestations of the disorder (Tierney 2010). As a result, therapies targeting the neurobehavioral component of SLOS are still needed.

In addition to cholesterol supplementation, bile acid supplementation has been advocated for neonates and children with cholestatic liver disease (Rossi 2005) and for those with severe disease manifestations of SLOS (Natowicz 1994; Nwokoro 1997; Svoboda 2012), despite the finding that most individuals with SLOS have normal levels of bile acids (Steiner 2000). Moreover, the physicians and parents of some children with SLOS give supplements of antioxidants, fat-soluble vitamins (e.g. vitamin E) or co-enzyme Q10 (coQ10) (or a

combination of these) in an attempt to augment their low levels expected in the disorder (Fliesler 2013; Fliesler 2018; Haas 2008; Korade 2014).

Normally, any cholesterol required for continuous fetal development after the first trimester, comes from endogenous sources i.e. has to be synthesized by the developing fetus. As a result, a failure to synthesize sufficient cholesterol occurs during the fetal period in SLOS, leading to an impaired synthesis of steroid hormones, bile acids, and cellular membranes, as well as abnormal central and peripheral nervous system myelination (Kelley 2000; Saher 2010; Woollett 2016). Additionally, cholesterol is a necessary co-factor in the post-translational modification and activation of various members of the hedgehog family of proteins, including sonic hedgehog (SHH), a key signalling molecule that orchestrates several pathways in fetal morphogenesis, especially brain development (Blassberg 2016; Cooper 2003; Kelley 2000; Porter 1996). At the same time, 7DHC whose levels are remarkably increased in individuals with SLOS, has also been shown to interfere with several of the downstream mediators or effectors of the SHH pathway (Kelley 2000; Koide 2006), thereby interfering with normal fetal development even further. In fact, defects in the SHH pathway have been associated with holoprosencephaly, a finding seen in some individuals with SLOS (Blassberg 2016; Haas 2010; Kelley 2000). Therefore, the ideal treatment goals in SLOS are to increase the levels of cholesterol and decrease those of 7DHC during fetal development, allowing for a normal activation of SHH signalling pathways and the synthesis of previously mentioned essential cholesterol-derived metabolites. Such an approach would likely prevent several of the neurobehavioral and cognitive abnormalities from developing in the first place, in individuals with SLOS. However, such a treatment approach is currently unavailable. Nonetheless, because neural and behavioral development continue to occur during the first five years of life, with continuous modulation by the external environment (Cao 2017; Jernigan 2011; Tierney 2009; Zoghbi 2003), interventions that increase cholesterol levels, or decrease 7DHC levels in infants with SLOS, or both, could improve or delay the onset of these cognitive and neurobehavioral abnormalities. Statins, pharmacological inhibitors of HMG-CoA reductase, the enzyme catalyzing the rate-limiting step of cholesterol biosynthesis, have been proposed as potentially promising candidates for that purposebased on the current understanding of the underlying biochemistry of SLOS. Specifically, by inhibiting HMG-CoA reductase, statins inhibit the synthesis of mevalonate, which lies upstream from most of the toxic cholesterol precursors implicated in SLOS pathogenesis such as 7DHC, thereby reducing the accumulation of these toxic compounds (Chan 2009; Jira 2000; Kelley 2000). Indeed, several animal studies and anecdotal reports in humans have demonstrated desired biochemical changes following statin use in SLOS: a reduction in the levels of 7DHC by inducing DHCR7 activity, and a paradoxical increase in the circulating levels of cholesterol (Correa-Cerro 2006; Haas 2007; Jira 2000; Svoboda 2012; Wassif 2005). Moreover, adding statins to cholesterol supplementation, compared to cholesterol supplementation alone, shows a more pronounced effect in lowering 7DHC levels and increasing circulating cholesterol levels (Chan 2009). Finally, while there are a number of statins available on the market, simvastatin has been the first choice of researchers in the field, being the most lipophilic of all available statins, and therefore, the one with the most likely ability to cross the BBB to exert its desired effects centrally, within the brain (Jira 2000).

How the intervention might work

The majority of cognitive and neurobehavioral abnormalities of SLOS are believed to result from a combination of a cholesterol deficit and 7DHC accumulation in utero, within the developing fetus (Kelley 2000). Cholesterol is integral to biological membranes, and a requirement for synthesizing bile acids, steroid hormones, and myelin. It is also required for the post-translational modification of several hedgehog signalling proteins, namely SHH (Kelley 2000).

Thus, an ideal treatment approach in SLOS entail supplementing the fetus with its much-needed deficient cholesterol, and reducing its 7DHC and 8DHC levels. However, this approach remains complex and is currently unavailable.

Alternatively, because neurodevelopment does not stop by birth, but instead continues postnatally, with various environmental factors modulating it, cholesterol supplementation, together with a reduction in levels of 7DHC and other neurotoxic cholesterol precursor molecules, may prove beneficial in promoting normal or near-normal postnatal development, allowing us to attenuate the neurobehavioral abnormalities that would otherwise most likely manifest more severely without any intervention. Indeed, starting cholesterol supplementation earlier has shown favorable effects in delaying the onset of ASD, or reducing their severity, in individuals with SLOS (Tierney 2001). Likewise, statins which inhibit HMG-CoA reductase, the enzyme that catalyzes the rate-limiting and regulatory step in the cholesterol biosynthesis pathway, have also been nominated as exerting possibly favorable biochemical changes in individuals with SLOS, particularly increasing cholesterol levels and reducing 7DHC levels (Jira 2000). Specifically, statins are thought to exert their beneficial biochemical effects in SLOS by way of inhibiting HMG-CoA reductase, thereby reducing the levels of mevalonate (Sotsman 1977) and all of its downstream metabolite precursors of cholesterol, including 7DHC and 8DHC, implicated in SLOS pathogenesis (Jira 2000). Statins have also been shown to increase the expression of DHCR7, while inducing the activity of the already available enzyme, in individuals with appreciable residual enzymatic activity (i.e. hypomorphic allele variants). This also leads to the favorable biochemical outcome of increased conversion of 7DHC to cholesterol (Correa-Cerro 2006; Wassif 2005).

Supporting a promising role of statin therapy in children with SLOS, several case reports published to date document favorable reductions in 7DHC levels and desired increases in plasma cholesterol levels, leading to enhanced growth and attenuated behavioral abnormalities (Haas 2007; Jira 2000; Porter 2008; Wassif 2005).

However, it is worth mentioning here the report on simvastatin treatment in an individual with severe SLOS arising from null biallelic mutations in her DHCR7 locus, which led to a worsening of her cholesterol deficit and photosensitivity, causing the authors of that study to conclude that beneficial effects of statin treatment are likely skewed in favor of only the individuals with sufficient residual DHCR7 activity that exceeds 5% that of normal (Starck 2002a). This point was then replicated in cell culture studies showing that fibroblasts with null mutations and remarkably diminished DHCR7 activity suffer profound toxicity and cell death following simvastatin treatment (Wassif 2005). These observations suggest, a priori,

an expected differential effect of statin treatment in SLOS between individuals with sufficient residual DHCR7 enzymatic activity (i.e., > 5% of normal), compared to those with very low or absent DHCR7 activity (i.e. < 5% of normal)

Why it is important to do this review

Despite being able to surgically correct and treat many of the congenital malformations and physical manifestations associated with SLOS, the vast majority of affected individuals continue to have variable neurobehavioral abnormalities that preclude normal development and functionality. The visceral malformations and physical manifestations of the disorder develop almost entirely prenatally, i.e. while the fetus is still developing in utero and fails to meet its own needs of endogenously-synthesized cholesterol required for normal organogenesis (Kelley 2000). However, because neurological and behavioral development persist beyond the fetal period and well into early childhood (Cao 2017; Tierney 2009; Zoghbi 2003), treatments that supplement cholesterol while reducing the accumulation of toxic cholesterol precursors such as 7DHC, may help alleviate and improve neurobehavioral outcomes in the long term (Jira 2000). Thus, we are conducting this systematic review to assess the efficacy of statins alone, or in combination with supplemental cholesterol, bile acids or antioxidants, compared with cholesterol supplementation alone (with or without supplementation with bile acids or antioxidants or both), in ameliorating the neurobehavioral abnormalities of individuals with SLOS. Moreover, we plan, if possible, to examine the differential effects of statin therapy in individuals with SLOS who have either the mild or typical disease severity with residual enzymatic activity exceeding 5% of normal, compared with those having the more severe phenotype with remarkably diminished enzyme activity (i.e. less than 5% that of controls). This review is especially important due to the current scarcity of data in this area, and the need for more evidence on the effects of statins on the neurobehavioral manifestations of individuals with SLOS.

OBJECTIVES

1. To evaluate the efficacy of statin therapy in reducing the frequency or severity of the neurobehavioral abnormalities seen in people with SLOS (e.g. aggression, anxiety, irritability, self-mutilation, autistic behaviors, sleep disturbances, etc.) (Wassif 2017).
2. To evaluate the potential effects of statin therapy on survival.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials: All randomized controlled trials (RCTs) or quasi-RCTs with parallel or cross-over designs will be included.

Non-randomized studies of interventions (NRSIs)

- Non-randomized clinical trials (controlled trials where allocation of the two groups is undertaken using methods other than randomization or quasi-randomization)
- Prospective cohort studies looking at neurobehavioral outcomes in people with SLOS taking a statin (with or without any of the other supplements (see 'Types of interventions'))
- Controlled before-after (pre-post) studies
- Studies with an interrupted-time-series (ITS) design may also be considered for inclusion, provided they satisfy the pre-set inclusion criteria detailed in the following sections.

We will include RCTs and NRSIs, as described above (EPOC 2017). The RCTs and NRSIs will not be pooled together; instead, we plan to conduct separate meta-analyses for the two categories of study design.

Types of participants—Adults and children diagnosed biochemically (i.e. through detecting elevated plasma levels of 7DHC in those not on drugs that can inhibit DHCR7 such as haloperidol, or through directly measuring DHCR7 enzyme activities in patient fibroblasts) or genetically (i.e. through molecular genetic testing) with SLOS, irrespective of age, sex, or disease severity, receiving any statin of any dosage or duration (Nowaczyk 2013; Shefer 1997).

We will exclude all studies that include individuals with other chronic comorbidities (metabolic or other genetic disorders) that can themselves affect cognition and behavior (i.e. confounders), as well as those individuals who cannot tolerate statins (i.e. those with statin hypersensitivity or severe statin-related side effects).

Types of interventions

1. Any statin (of any dosage or duration) alone, versus cholesterol supplementation only
2. Any statin (of any dosage or duration) combined with cholesterol supplementation, versus cholesterol supplementation only (Chan 2009)
3. Any statin (of any dosage or duration) with or without bile acid supplementation, versus cholesterol supplementation alone or in combination with bile acid supplementation
4. Any statin (of any dosage or duration) with or without any or all of: coenzyme Q10, vitamins E, A, or C, or other antioxidants (e.g. selenium) (or both), versus cholesterol supplementation alone or in combination with all or any of these vitamins and antioxidants (Fliesler 2013; Fliesler 2018; Korade 2014)
5. Lipophilic statins (e.g. simvastatin, lovastatin, pitavastatin, or atorvastatin) versus hydrophilic statins (e.g. pravastatin or rosuvastatin)

We will exclude studies administering two or more statins, i.e. combined-statin therapy, due to the inability to attribute causality to a particular statin agent especially when using a lipophilic and hydrophilic statin combination. However, we will include studies in which an individual has received more than one statin, provided that there has been an adequate washout interval of at least four weeks between the discontinuation of the first statin and introduction of another one.

Types of outcome measures

Primary outcomes

1. Survival
    a. Overall survival covering all SLOS (see below) and non-SLOS-related deaths such as accidents, other genetic or metabolic conditions (e.g. diabetic ketoacidosis), prematurity, etc.
    b. SLOS-related deaths specifically, which include those deemed by the investigators of individual studies as having been most likely a direct result of having SLOS or one of its features or manifestations (e.g. due to overwhelming infections not otherwise explained by an underlying immunodeficiency, severe malnutrition requiring parenteral feeding that is followed by sepsis, severe feeding problems and malnutrition due to gastrointestinal abnormalities related to SLOS, or death from severe visceral (especially cardiac and renal) or brain malformations) (Nowaczyk 2013)
2. Changes in the severity or frequency of neurobehavioral abnormalities (assessed by comparison with each individual's corresponding baseline, i.e. at the time of initial enrolment in the study)
    a. Anxiety (evaluated using, e.g. the Pediatric Anxiety Rating Scale (PARS)) (The Pediatric Anxiety Rating Scale (PARS) 2002)
    b. Attention-deficit hyperactivity disorder (ADHD) (evaluated using, e.g. the Conner's Continuous Performance Test (CCPT) or the Test of Variables of Attention (TOVA)) (Edwards 2007)
    c. Pro-active aggression against others or self (i.e. self-mutilation) (assessed using, e.g. the Buss-Perry Aggression Questionnaire (BPAQ) and the Functional Assessment of Self-Mutilation (FASM) tools) (Buss 1992; Lloyd 1997)
    d. Emotional lability (e.g. tantrums or aggressive outbursts to obtain tangible objects, i.e. reactive aggression), or agitation, or irritability (assessed using, e.g. the Emotion Regulation Checklist (ERC) or the irritability subscale of the Aberrant Behavior Checklist-Community (ABC-C) tools) (Aman 1995; Shields 1997)

e. Sleep disturbances (evaluated using, e.g. the Pediatric Sleep Questionnaire (PSQ) or the Children's Sleep Habits Questionnaire tools) (Chervin 2000; Owens 2000)

f. ASD (evaluated using, e.g. the Autism Diagnostic Observational Schedule (ADOS)) (Lord 2001)

3. Statin-related adverse reactions

   a. Liver-related: hepatotoxicity assessed by liver function tests (defined as having SGOT or SGPT levels (or both) at or exceeding three times the upper limit of normal (ULN)) (Rosenson 2019a)

   b. Muscle-related: myalgias (self-reported by patients or their caregivers or both), myopathy (defined as elevations in the levels of creatine phosphokinase (CPK) often to 10 times the ULN (Starck 2002a), or aldolase, or lactate dehydrogenase (LDH), or any combination of these parameters), or rhabdomyolysis (Rosenson 2019b)

   c. Skin-related: increased or worsening photosensitivity following statin initiation (measured quantitatively as UV-A tolerance in joules/cm^2) (Starck 2002a; Starck 2002b)

   d. Others: depletion of or reduction in CoQ10 levels (Qu 2018; Rundek 2004), or developing rare adverse reactions such as cognitive dysfunction, sleep disturbances, abdominal pain, diarrhea or neuropathy (Haas 2007; Rosenson 2019a; Wassif 2017).

Secondary outcomes

1. Changes in the growth parameters of children during or after statin treatment (for at least two years in adolescents (males and females who attained puberty) and up to 10 years in prepubertal children and those under the age of 10 years)

   a. Height

   b. Weight

   c. Head circumference

   d. Body mass index (BMI)

   e. Tanner staging

2. Changes in the biochemical markers of the disorder

   a. Plasma lipid levels (total cholesterol, LDL-C, HDL-C, apoA-I, and apoB) (Olah 2013)

   b. Vitamin D levels (25-hydroxy and 1, 25-dihydroxy forms)

   c. Oxysterols

d. Plasma or cerebrospinal fluid (CSF) levels (or both) of 7DHC or 8DHC or other dehydrosterols (reported preferably as ratios of total sterols) (Kelley 2000; Olah 2013)

e. Any other markers such as the levels of CoQ10, vitamin E, plant sterols, etc.

3. Quality of life (QoL) (measured by, e.g. validated instruments or scales or health outcome rating scales, or self-reported satisfaction or dissatisfaction) including feeding behavior or tolerance

Search methods for identification of studies

We will search for all relevant published and unpublished trials without restrictions on language, year of publication, or publication status.

For studies published in languages non-native to the authors, we will consult with the National Institutes of Health (NIH) translation services for assistance in translating those references.

Electronic searches—The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist will conduct a search of the Group's Cystic Fibrosis Trials Register for relevant trials using the following terms: Lemli or Opitz.

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 Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

We will also search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (www.cochranelibrary.com/);
- PubMed (www.ncbi.nlm.nih.gov/pubmed) (1946 to present);
- Embase.com (1982 to present);
- Web of Science (WoS) Core Collection covering Science Citation Index Expanded (1900 to present), Social Sciences Citation Index (1900 to present), Conference Proceedings Citation Index-Science (1990 to present), Book Citation Index-Science (2005 to present), Emerging Sources Citation Index (2005 to present), SciELO Citation Index (https://clarivate.com/products/web-of-science/databases/) (2002 to present);
- Scopus (1823 to present);

- LILACS (Latin American and Caribbean Health Science Information Database) (https://lilacs.bvsalud.org/en/) (1982 to present);
- CRD (Centre for Reviews and Dissemination) Database (www.crd.york.ac.uk/CRDWeb/);
- PROSPERO (International Prospective Register of Systematic Reviews) (www.crd.york.ac.uk/PROSPERO/);
- NARCIS (National Academic Research and Collaborations Information system) (www.narcis.nl/);
- OpenGrey (www.opengrey.eu/).

Additionally, we will search the following trial registries.

- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch);
- EU Clinical Trials Register (www.clinicaltrialsregister.eu).

For details of our search strategies please refer to the appendices (Appendix 1).

Searching other resources—We will handsearch the abstracts and conference proceedings of the Society for Inherited Metabolic Disorders (SIMD).Theseare available online as supplements to the Molecular Genetics and Metabolism journal (MGM) and we will check all years (1998 to present) for online availability.

We will also search the Sterol and Isoprenoid Research Consortium (STAIR) of the National Institutes of Health's Rare Disease Clinical Research Network (NIH RDCRN) for any ongoing work in SLOS relevant to our review (www.rarediseasesnetwork.org/cms/stair).

The reference lists of all included articles and relevant systematic reviews will be reviewed to identify additional studies not found through electronic searching.

Data collection and analysis

Selection of studies—Two review authors (RB and SB) will independently and in duplicate screen the titles and abstracts of all references retrieved by the searches, evaluating their relevance to our review question. However, prior to the title and abstract screening stage, the two authors will undergo a calibration exercise, in the presence of a third person, to ensure screening consistency amongst them.

The same authors (RB and SB) will then retrieve and screen, in duplicate and independently, the full text versions of all references deemed possibly eligible by at least one of them during the antecedent title and abstract screening stage. Wherever we encounter disagreements, we will resort to discussion among them first for resolution. In cases where consensus cannot be attained through discussion, we will consult with the expert member of the team (FP) for resolution.

As per chapter 7 (Table 7.2) of the *Cochrane Handbook for Systematic Reveiws of Interventions*, we will calculate a simple kappa statistic at the end to indicate the extent of inter-reviewer agreement with regards to full-text screening (Higgins 2011a).

Data extraction and management—Two review authors (RB and SB) will independently and in duplicate extract relevant data from the included studies, utilizing the data extraction tool within Review Manager software (RevMan 2014). We will extract data on the following.

1. Study characteristics (author, country, publication year, study design, duration of study, funding, and conflicts of interest).
2. Participant characteristics (age and sex distribution along with the study-defined inclusion and exclusion criteria, noting how participants were selected or randomized).
3. Numbers of participants enrolled in each arm, with their attrition rates (where applicable).
4. Details of the intervention(s) and their control(s) and comparator(s) (e.g. dosage and duration of statin or cholesterol replacement therapies).
5. Outcomes measured by each study.
6. Notes on any special considerations that should be taken into account with regards to a particular study, including how potential confounders (e.g. ethnicity or race (Benjamin 2018), diet, disease severity) were handled in NRSI.

For the survival outcome, we plan to present data at 6, 12, 24, and 36 months and annually thereafter. For all other outcomes, we plan to group outcome data into those measured at 2, 6 and 12 months and annually thereafter. However, if investigators record relevant outcome data at other time periods, we will consider presenting these as well.

The two authors aim to resolve any disagreements through discussion and will resort to the opinion of the team's expert (FP) after failing to reach consensus. Should we encounter any missing, unclear, or incomplete data, we will make reasonable attempts to contact the corresponding author(s) of the studies in question for further clarification. When more than a single report are published for the same study, we will ensure that all data across all of the reports are included in our review.

The lead author (RB) will enter all extracted data into Review Manager software (RevMan 2014) which will be reviewed by the team's biostatistician (YF) for confirmation.

Assessment of risk of bias in included studies—Two authors (RB and SB) will independently assess the overall risk of bias for each of the included studies using the relevant risk of bias assessment tool(s) outlined below. We will resolve any disagreement(s) by discussion or by consulting with a third author (FP).

RCTs: For RCTs, we will use the risk of bias assessment tool outlined in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will then summarize their combined assessments in Review Manager software (RevMan 2014).

We will assess the risk of bias of RCTs in a six-domain-based 'Risk of Bias' table that appraises the following methodological and validity domains.

1. Random sequence generation (selection bias).
2. Allocation concealment (i.e. concealing participant allocation prior to assignment) (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (i.e. high rates of attrition, or improper handling or reporting (or both) of incomplete outcome data) (attrition bias).
6. Selective outcome reporting (i.e. non-adherence to pre-set protocol) (reporting bias).
7. Other biases possibly arising from issues not covered or addressed elsewhere in the table.

We will judge each domain of bias as having a 'high risk', 'low risk' or 'unclear risk' of bias, including a supporting quotation or statement from the study together with a narrative justification of our corresponding judgment within the 'Risk of bias' table.

NRSIs, Cohort or ITS studies: For all non-RCTs, we will use the ROBINS-I tool (i.e. Risk Of Bias In Non-randomized Studies of Interventions) to evaluate the risk of bias in estimates of the comparative effectiveness of interventions, and rate the overall quality of non-RCT studies (Sterne 2016). The tool uses 'signalling questions' to rate the risk of bias judgement as 'low', 'moderate', 'serious', or 'critical', or alternatively, 'no information' when insufficient information is present for a particular domain. We will use the tool to assess seven distinct domains of non-RCTs that are listed below.

1. Bias due to confounding (e.g. ethnicity or race, diet, disease severity).
2. Bias in the selection of participants into the study.
3. Bias in classification of interventions.
4. Bias due to deviations from intended interventions (with intention-to-treat (ITT) analyses being preferred, wherever reported).
5. Bias due to missing data.
6. Bias in measurement of outcomes.
7. Bias in the selection of the reported result.

When ROBINS-I fails to adequately cover certain aspects of cohort studies or ITS studies, we will use the following criteria outlined in the Newcastle-Ottowa Scale (NOS) (NOS

2019) to assess the risk of bias in cohort studies, or the subsequent criteria listed by EPOC reviews (EPOC 2017) for ITS studies.

Cohort studies (using the NOS)

1. Was the selected cohort representative of the target population?
2. Was selection of exposed and non-exposed cohorts drawn from the same population?
3. Can we be confident in the assessment (i.e. ascertainment) of exposure?
4. Can we be confident that the outcome of interest was not present at start of study?
5. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest (i.e. comparability of the different cohorts) or did the statistical analysis adjust for these prognostic variables?
6. Can we be confident in the assessment of outcome?
7. Was the follow up long enough?
8. Was there adequate follow up of cohorts to minimize attrition rates?

ITS studies (using EPOC criteria)

1. Was the intervention independent of other changes?
2. Was the shape of the intervention effect pre-specified?
3. Was the intervention unlikely to affect data collection?
4. Was knowledge of the allocated interventions adequately prevented during the study?
5. Was incomplete outcome data adequately addressed?
6. Was the study free from selective outcome reporting?
7. Was the study free from other risks of bias?

Measures of treatment effect

1. **RCTs—**For dichotomous data, e.g. adverse drug reactions (ADRs), we will report the number of participants experiencing the event relative to the total number of participants evaluated for that outcome, thereby reporting risk ratios (RRs) (preferably) or risk differences (RDs) (less preferred) as effect measures with their corresponding 95% confidence intervals (95% CIs), depending on the data reported by each included study.

For continuous data, e.g. anthropometric measures or quantitative ADRs (such as CPK, aldolase, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), or liver enzyme levels), we will report the mean differences (MDs) or standardized mean differences (SMDs) as effect measures with their corresponding 95% CIs. We will use MDs when all relevant trials measure the same outcome of interest using a comparable or identical scale or

standard, while using SMDs when relevant trials measure the same outcome of interest using different or incomparable instruments or scales. If not directly reported, we will attempt to use any of the available reported data to derive the required SMD (where applicable), using ITT analysis with imputation.

If and when SMDs are generated, they will be interpreted using the rules of thumb established mainly by researchers in the social sciences, such that an SMD of 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen 1988). Variations still exist however (e.g. < 0.40 = small, 0.40 to 0.70 = moderate, > 0.70 = large). As such, some methodologists believe that such interpretations are problematic because patient importance of a finding is context-dependent and not amenable to generic statements. A transformation of a SMD to a (log) odds ratio can be pursued in that instance, based on the assumption that an underlying continuous variable has a logistic distribution with equal standard deviation in the two intervention groups (Chinn 2000; Furukawa 1999). Such an assumption is unlikely to hold precisely, so the generated results must be regarded only as an approximation. The log odds ratio can be estimated as: lnOR = 1.81×SMD approximately.

2. NRSIs—For dichotomous outcomes, if available, we will report the RR or RD with 95% CI adjusted for baseline differences (such as Poisson regressions or logistic regressions), or the ratio of RRs (i.e. the RR post-intervention / RR pre-intervention), depending on the data reported by each included study.

For continuous variables, if available, we will report the absolute change adjusted for baseline differences (such as regression models, mixed models or hierarchical models) or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups / the post-intervention level in the control group).

For time-to-event data (i.e. ITS studies) that take into account the number and timing of events (e.g. overall survival at different years), or survival outcomes in general, we plan to summarize and analyze the data using hazard ratios (HRs) and their corresponding 95% CIs (Higgins 2011).

For studies not reporting change-from-baseline data, i.e. those presenting only absolute post-treatment data without baseline data (so it is not possible to calculate change data), we will consider, if appropriate, reporting the absolute post-treatment data instead of change from baseline. However, we will combine such studies together and separate from ones that entail change data.

Finally, for all other outcomes with insufficient data to perform a quantitative analysis, or alternatively, wherever such an analysis is not possible (such as QoL or behavioral progression parameters (or both)), we will narratively summarize the study data.

Unit of analysis issues

Given that we may include RCTs, non-RCTs, cohort studies, and ITS studies in this review, we might encounter unit of analysis issues in the following situations:

1. groups of individuals were randomized together to the same intervention (i.e. cluster-randomized trials);
2. individuals undergo more than one intervention (e.g. in a cross-over trial);
3. there are multiple observations for the same outcome (e.g. repeated measurements, recurring events, etc.).

Therefore, should we include any of these study designs in our review, we will treat these in accordance with the advice given in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* as summarized below (Higgins 2011c).

1. For cluster designs, we will extract results adjusted for clustering, and if the reported analyses have not been already adjusted for clustering, we will re-analyze the data taking clustering into account (wherever such an analysis is possible). If adjustment is not possible we will present the data in a table.
2. For studies in which participants are randomized more than once, we will make reasonable attempts to contact the authors of these studies to provide us with the data on outcomes associated with the initial randomization.
3. For studies with multiple treatment groups we will include subgroups that are considered relevant to the analysis and clinically reasonable choices. When appropriate, we will combine groups to create a single pair-wise comparison. If this is not possible, we will select the most appropriate pair of interventions and exclude the others (Higgins 2011c).
4. Any other unit of analysis issues arising from the inclusion of ITS studies we will process these according to the EPOC recommendations ((EPOC 2017).
5. For cross-over trials we will restrict the analysis to only the instances where a carry-over effect of the intervention is known to be very minimal or negligible across the different time periods (Elbourne 2002). In our case, we have predetermined that eligible studies with cross-over designs have to employ a washout period of at least four weeks (Henriques-Forsythe 2015) and preferably six or more weeks (McGowan 2004) since statin therapy discontinuation, to ensure that the effects of the latter have completely subsided from the body prior to instituting any other intervention such as cholesterol supplementation, switching to a different statin, or starting antioxidant(s) or vitamin(s) administration (or both). In such cases, we will use a paired analysis for analysing cross-over trials data if at least one of the following conditions is met:
    a. individual participant data from the paper or by correspondence with the trial author (i.e. investigator);

b. the mean and standard deviation (or standard error) of the participant-specific differences between experimental intervention (E) and control intervention (C) measurements;

c. the MD and one of the following: (i) a t-statistic from a paired t-test; (ii) a P value from a paired t-test; (iii) a CI from a paired analysis;

d. a graph of measurements on experimental intervention (E) and control intervention (C) from which individual data values can be extracted, as long as matched measurements for each individual can be identified as such.

6. For studies with multiple observations per participant, we will attempt to use the following strategies to conduct their analysis:

a. obtain individual patient data (IPD) and perform an analysis (such as time-to-event analysis) that uses the whole follow-up for each participant;

b. compute an effect measure for each individual participant which incorporates all time points, such as total number of events, an overall mean, or a trend over time;

c. select a single time point and analyze only data at this time for studies in which it is presented.

Dealing with missing data

We will make reasonable attempts to contact the corresponding authors of eligible studies for any missing, unclear, or incomplete data, primarily with trials reporting means without their corresponding standard deviations (SDs). However, in cases where we fail to obtain the required information, we will attempt to calculate the missing data using the available (i.e. reported) data, such as calculating a SD based on the reported CIs, means, and number of participants.

Assessment of heterogeneity

We will assess the methodological variability (i.e. statistical heterogeneity) across the included trials using both, the visual or 'eye-rolling' approach where we visually assess the degree of overlap between the CIs of the different studies in our forest plot, and quantitatively, through calculating a formal I^2 statistic which estimates the percentage of total variation observed across studies due to methodological variability rather than sampling (i.e. random) error(s) (Higgins 2003).

We will then grade the degree of heterogeneity involved based on the generated I^2 statistic into: no heterogeneity (I^2: 0% to 24%), low-degree heterogeneity (I^2: 25% to 49%), moderate-degree heterogeneity (I^2: 50% to 74%), and high-degree heterogeneity (I^2: greater than or equal to 75%) (Higgins 2003).

Wherever we encounter remarkable statistical heterogeneity (i.e. moderate or high degree), we shall attempt to identify its source(s) through conducting relevant subgroup analyses, with the aim of identifying possible sources of bias or methodological differences.

We will analyze the data extracted from included studies based on an ITT analysis when effect estimates are not directly reported.

Assessment of reporting biases

We will examine funnel plots to identify any reporting biases, such as publication, language, time-lag, or location biases, only if there are at least five relevant trials published in the literature. The reason we have selected five studies instead of the conventional 10 as a 'cut-off' for when to analyse publication or reporting bias is the rarity of the condition *per se* and the investigators involved in researching the disease. In that case, the funnel plot will exhibit asymmetry if reporting biases exist, for which we shall probe any discernible underlying causes. A number of causes can lead to an asymmetrical funnel plot such as the inherently different methodological qualities of small studies compared to larger ones ('small-study effects'), the presence of true heterogeneity, remarkable time lapse between the conduction of small trials and larger ones (i.e. time-lag bias), language bias, or simply chance (Sterne 2011).

Data synthesis

RCTs—If meta-analysis for RCTs is possible, we will analyze these as per chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We will be using RevMan version 5.3 to conduct the statistical analyses of our extracted data (RevMan 2014). We will use a random-effects model to meta-analyze trial data, given the likelihood that the studies addressing our question are heterogeneous due to the rarity of the disease itself, and consequently, the anticipated paucity of relevant trials, along with our expectation of the existence of variable effects (such as differences in response to treatment) among the different patients (due to age, sex, and disease severity) (Riley 2011).

However, we will not perform any meta-analyses for trials with an insufficient similarity of populations, interventions, or methods, or those for whom we cannot explain an existent substantial heterogeneity neither through subgroup analyses nor by individually assessing the methodologies employed by those studies. In that case, we shall resort to narratively reporting the data only.

NRSIs—If meta-analysis is feasible for NRSIs, we will analyze these separately, as per chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011).

However, while assessing NRSIs prior to meta-analysis, we will examine features of these studies for homogeneity and risk of bias. If we decide that included NRSIs are both reasonably resistant to biases and relatively homogeneous, we will combine data across studies in a meta-analysis with adjusted effect estimates to control for confounding effects (Taggart 2001). We can perform meta-analysis of adjusted estimates using an inverse-variance weighted average, e.g. using the 'generic inverse-variance' outcome type in

RevMan, as per chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). If included NRSIs are not sufficiently homogeneous to combine in a meta-analysis, we will display results of included studies in a forest plot suppressing the pooled estimate, as well as additional tables with a systematic format.

Subgroup analysis and investigation of heterogeneity

If adequate data are available, we will attempt to address any heterogeneity that emerges for an outcome, among any pooled group of included studies (RCTs and NRSIs to be analysed separately), by conducting the following subgroup analyses:

1. the effects of disease severity on survival (i.e., among 'mild' versus 'classical or typical or moderate' versus 'severe' SLOS)*;
2. the effects of low (reduction in LDL-C by < 30%) versus moderate (reduction in LDL-C by < 50% and > 30%) versus high (reduction in LDL-C by > 50%; primarily atorvastatin or rosuvastatin) intensity statin therapy (ACC/AHA 2014; Stone 2014);
3. the effects of age (pediatric (1 to 18 years of age) versus adults (over 18 years of age)) and sex (males versus females);
4. the effects of the chemical nature of the statin used, i.e. lipophilic (simvastatin, lovastatin, pitavastatin, or atorvastatin) versus hydrophilic (pravastatin or rosuvastatin) statins (Bytyçi 2017);
5. the effects of different formulations, dosages, or durations of cholesterol or bile acid supplementation, alone or in combination with statins (Nowaczyk 2013);
6. the effects of markedly diminished residual DHCR7 enzymatic activity (i.e., less than 5%; usually in the severe forms of the syndrome) versus moderately reduced residual enzymatic activity (i.e., greater than or equal to 5% the activity of normal; usually in the mild and typical forms of the syndrome) (Starck 2002a).

*defined based on the severity of their physical manifestations into 'mild' (a score of less than 20), 'moderate' or 'classic' or 'typical' (a score of 20 to 50), or 'severe' (a score of more than 50) (Bialer 1987; Kelley 2000).

Sensitivity analysis—If at least five studies are included in the review, we will perform a sensitivity analysis to test for the robustness of the generated data by excluding trials with an overall high risk of bias and seeing how that affects the overall pooled effect estimates for each outcome of interest. We will then compare the estimates generated by such sensitivity analyses to those generated when all relevant studies were pooled together irrespective of quality.

Summary of findings and quality of the evidence (GRADE): Two review authors will independently and in duplicate assess the overall quality of evidence for the six outcomes listed below, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the *GRADE Handbook* (Schünemann 2013).

1. Overall survival at 6, 12, 24, and 36 months
2. Changes (improvement or exacerbations) in any of the neurobehavioral manifestations during the study period
3. Statin-related adverse reactions (hepatotoxicity and myalgias or myopathy)
4. Negative changes in the growth parameters of children receiving a statin (e.g. falling off their baseline growth curve for height or weight)
5. Changes in the biochemical markers of the disorder during treatment
6. QoL

We will create separate summary of findings tables for RCTs and NRSIs, as follows.

RCTs—We will consider the starting quality of evidence for RCTs as 'high quality' and then downgrade it by one or two levels for serious and very serious limitations respectively, based on: the individual quality of each study (i.e. risk of bias), the degree of consistency across studies, the extent of directness of the reported evidence, the precision of estimates, and the presence of publication bias.

NRSIs—Contrary to the case with RCTs, we will consider the starting quality of evidence for non-RCTs as 'low quality' when NOS is used to assess the risk of bias, and then upgrade it by one or two levels for adequately demonstrating certain criteria such as: large effect size, a dose-response associations, or seeing an effect in the presence of confounders that would usually 'mask' or reduce the likelihood of seeing an effect. In contrast, for NRSI in which ROBINS-I could be used, we will consider the starting quality of evidence as 'high quality' and then rate it down in the presence of serious concerns and limitations such as: indirectness of evidence, heterogeneity, imprecision, or publication bias (Schünemann 2018).

We will then use the Guideline Development Tool to create a 'Summary of findings' (SoF) table to report the overall quality of evidence for each outcome of interest (clinical relevance) (GRADEpro 2011). We will then justify all our decisions with regards to downgrading or upgrading the quality of evidence using footnotes, and additional comments available to reader where necessary.

The GRADE approach results in assignment of the quality of a body of evidence to one of four grades, defined below.

1. High: we are very confident that the true effect lies close to the generated effect estimate.
2. Moderate: we are moderately confident in the effect estimate such that the true effect is likely to be close to the generated effect estimate but may be substantially different.
3. Low: we have limited confidence in the effect estimate such that the true effect may be substantially different from the generated effect estimate.

4. Very low: we have very little confidence in the effect estimate such that the true effect is likely to be substantially different from the generated effect estimate.

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APPENDICES

Appendix 1.

Search Methods - Electronic Searching

Database/ Resource	Strategy
CENTRAL in the Cochrane Library	#1 MeSH descriptor: [Smith-Lemli-Opitz Syndrome] explode all trees
	#2 lemli OR opitz OR SLO OR SLOS OR "cholesterol deficiency" OR "cholesterol deficient" OR "cholesterol deficiencies" OR RSH OR "Lethal Multiple Congenital Anomaly Syndrome" OR "Lethal Acrodysgenital" OR "7 Dehydrocholesterol Reductase" OR DHCR7 OR "7 dehydrocholesterol reductase" OR "7 dehydrocholesterol delta 7 reductase" OR "3beta hydroxysterol delta 7 reductase" OR "NADPH sterol delta 7 reductase"
	#3 #1 OR #2
	#4 MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
	#5 MeSH descriptor: [Hydroxymethylglutaryl CoA Reductases] explode all trees
	#6 MeSH descriptor: [Atorvastatin] explode all trees
	#7 MeSH descriptor: [Fluvastatin] explode all trees
	#8 MeSH descriptor: [Lovastatin] explode all trees
	#9 MeSH descriptor: [Rosuvastatin] explode all trees
	#10 MeSH descriptor: [Meglutol] explode all trees
	#11 MeSH descriptor: [Pravastatin] explode all trees
	#12 MeSH descriptor: [Simvastatin] explode all trees
	#13 Statin OR statins OR Atorvastatin* OR Liptonorm OR Lipitor OR atorlip OR aplactin OR atovarol OR glustar OR lowlipen OR sortis OR storvas OR tahor OR torvast OR zarator OR bervastatin OR cerivastatin OR crilvastatin OR dalvastatin OR fluvastatin* OR Fluvastatinum OR fluindostatin OR lescol OR canef OR cranoc OR lochol OR locol OR vastin OR glenvastatin OR lovastatin OR monacolin OR Mevinolin* OR Mevacor OR altocor OR altoprev OR artein OR belvas OR cholestra OR lipdip OR lipivas OR lostatin OR lovalip OR lovalord OR lovasterol OR lovastin OR lozutin OR mevinacor OR nergadan OR rodatin OR rovacor OR taucor OR meglutol OR mevastatin OR compactin OR mevastin OR medostatin OR Pitavastatin OR nisvastatin OR itavastatin OR Itavastin OR alipza OR livalo OR livazo OR pitava OR vezepra OR pravastatin OR eptastatin* OR epatostantin OR epistatin OR fluindostatin OR vasten OR lipemol OR liplast OR prareduct OR mevalotin OR pravachol OR pralidon OR elisor OR selektine OR pravacol OR lipostat OR baycol OR bristacol OR astin OR epatostantin OR eptastatine OR lipidal OR liprevil OR prastan OR pravaselect OR pravasin OR pravator OR sanaprav OR selipran OR Rosuvastatin OR crestor OR rosuvas OR Simvastatin OR Synvinolin OR Zocor OR cholestat OR colastatina OR covastin OR denan OR epistatin OR eucor OR ifistatin OR klonastin OR kolestevan OR lipex OR lipinorm OR lipovas OR lodales OR medipo OR rechol OR simcard OR simovil OR simvacor OR simvatin OR simvor OR simvotin OR sinvacor OR sinvastatin OR sivastin OR valemia OR Velastatin OR vasilip OR vasotenal OR zocord OR zovast OR tenivastatin OR "HydroxymethylglutarylCoA Reductase Inhibitor" OR "HydroxymethylglutarylCoA Reductase Inhibitors" OR "Hydroxymethylglutaryl coenzyme A Reductase Inhibitor" OR "Hydroxymethylglutaryl coenzyme A Reductase Inhibitors" OR "HMG CoA" OR HMGcoA OR "HMG co a" OR "beta Hydroxy beta Methylglutarate" OR "3 Hydroxy 3 methylglutaric Acid" OR "HMGcoenzyme A" OR "3hydroxy3methylglutarylCoA" OR "3hydroxy3methylglutarylcoenzyme A" OR "HMG CoA reductase inhibitor" OR "HMG CoA reductase inhibitors" OR "hmg coenzyme a reductase inhibitor" OR "hmg coenzyme a reductase inhibitors" OR "Anticholesteremic Agent" OR "Anticholesteremic Agents" OR "HydroxymethylglutarylCoA Reductases"
	#14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13

Database/ Resource	Strategy
	#15 #3 AND #14
PubMed	(“Smith-Lemli-Opitz Syndrome”[Mesh] OR lemli[tw] OR opitz[tw] OR SLO[tw] OR SLOS[tw] OR “cholesterol deficiency”[tw] OR “cholesterol deficient”[tw] OR “cholesterol deficiencies” OR RSH[tw] OR “Lethal Multiple Congenital Anomaly Syndrome”[tw] OR “Lethal Acrodysgenital”[tw] OR “7-Dehydrocholesterol Reductase”[tw] OR DHCR7[tw] OR 7-dehydrocholesterol reductase[Supplementary Concept] OR “7 dehydrocholesterol delta 7 reductase”[tw] OR “3beta hydroxysterol delta 7 reductase”[tw] OR “NADPH-sterol delta 7-reductase”[tw]) AND (Statin[tw] OR statins[tw] OR Atorvastatin*[tw] OR Liptonorm[tw] OR Lipitor[tw] OR atorlip[tw] OR aplactin[tw] OR atovarol[tw] OR glustar[tw] OR lowlipen[tw] OR sortis[tw] OR storvas[tw] OR tahor[tw] OR torvast[tw] OR zarator[tw] OR bervastatin[tw] OR cerivastatin[tw] OR crilvastatin[tw] OR dalvastatin[tw] OR fluvastatin*[tw] OR Fluvastatinum[tw] OR fluindostatin[tw] OR lescol[tw] OR canef[tw] OR cranoc[tw] OR lochol[tw] OR locol[tw] OR vastin[tw] OR glenvastatin[tw] OR lovastatin[tw] OR monacolin[tw] OR Mevinolin*[tw] OR Mevacor[tw] OR altocor[tw] OR altoprev[tw] OR artein[tw] OR belvas[tw] OR cholestra[tw] OR lipdip[tw] OR lipivas[tw] OR lostatin[tw] OR lovalip[tw] OR lovalord[tw] OR lovasterol[tw] OR lovastin[tw] OR lozutin[tw] OR mevinacor[tw] OR nergadan[tw] OR rodatin[tw] OR rovacor[tw] OR taucor[tw] OR meglutol[tw] OR mevastatin[tw] OR compactin[tw] OR mevastin[tw] OR medostatin[tw] OR Pitavastatin[tw] OR nisvastatin[tw] OR itavastatin[tw] OR Itavastin[tw] OR alipza[tw] OR livalo[tw] OR livazo[tw] OR pitava[tw] OR vezepra[tw] OR pravastatin[tw] OR eptastatin*[tw] OR epatostantin[tw] OR epistatin[tw] OR fluindostatin[tw] OR vasten[tw] OR lipemol[tw] OR liplast[tw] OR prareduct[tw] OR mevalotin[tw] OR pravachol[tw] OR pralidon[tw] OR elisor[tw] OR selektine[tw] OR pravacol[tw] OR lipostat[tw] OR baycol[tw] OR bristacol[tw] OR astin[tw] OR epatostantin[tw] OR eptastatine[tw] OR lipidal[tw] OR liprevil[tw] OR prastan[tw] OR pravaselect[tw] OR pravasin[tw] OR pravator[tw] OR sanaprav[tw] OR selipran[tw] OR Rosuvastatin[tw] OR crestor[tw] OR rosuvas[tw] OR Simvastatin[tw] OR Synvinolin[tw] OR Zocor[tw] OR cholestat[tw] OR colastatina[tw] OR covastin[tw] OR denan[tw] OR epistatin[tw] OR eucor[tw] OR ifistatin[tw] OR klonastin[tw] OR kolestevan[tw] OR lipex[tw] OR lipinorm[tw] OR lipovas[tw] OR lodales[tw] OR medipo[tw] OR rechol[tw] OR simcard[tw] OR simovil[tw] OR simvacor[tw] OR simvatin[tw] OR simvor[tw] OR simvotin[tw] OR sinvacor[tw] OR sinvastatin[tw] OR sivastin[tw] OR valemia[tw] OR Velastatin[tw] OR vasilip[tw] OR vasotenal[tw] OR zocord[tw] OR zovast[tw] OR tenivastatin[tw] OR “Hydroxymethylglutaryl-CoA Reductase Inhibitors”[tw] OR “Hydroxymethylglutaryl coenzyme a Reductase Inhibitor” [tw] OR “Hydroxymethylglutaryl coenzyme a Reductase Inhibitors”[tw] OR “Hydroxymethylglutaryl-CoA Reductase Inhibitors”[tw] OR “HMG CoA”[tw] OR HMGcoA[tw] OR “HMG-coA”[tw] OR “HMG-co-A”[tw] OR “beta Hydroxy beta Methylglutarate”[tw] OR “3 Hydroxy 3 methylglutaric Acid”[tw] OR HMG-CoA[tw] OR “HMG-coenzyme A”[tw] OR “3-hydroxy-3-methyl-glutaryl-CoA”[tw] OR “3- hydroxy-3-methylglutaryl-coenzyme A”[tw] OR “HMG CoA reductase inhibitor”[tw] OR “HMG CoA reductase inhibitors”[tw] OR “hmg coenzyme a reductase inhibitor”[tw] OR “Atorvastatin”[Mesh] OR “Fluvastatin”[Mesh] OR “Lovastatin”[Mesh] OR “Rosuvastatin Calcium”[Mesh] OR “Meglutol”[Mesh] OR “Pravastatin” [Mesh] OR “Simvastatin”[Mesh] OR atorvastatin[Substance Name] OR fluvastatin[Substance Name] OR pitavastatin[Supplementary Concept] OR “Anticholesteremic Agents” [Pharmacological Action] OR “Hydroxymethylglutaryl CoA Reductases”[Mesh] OR “Hydroxymethylglutaryl- CoA Reductase Inhibitors” [Pharmacological Action] OR “Hydroxymethylglutaryl-CoA Reductase Inhibitors”[Mesh] OR “3-hydroxy-3-methylglutaryl-coenzyme A”[Supplementary Concept])
Embase.com	(‘Smith Lemli Opitz syndrome’/exp OR ‘7 dehydrocholesterol reductase’/exp OR lemli:ab,ti OR opitz:ab,ti OR SLO:ab,ti OR SLOS:ab,ti OR “cholesterol deficiency”:ab,ti OR “cholesterol deficiencies”:ab,ti OR “cholesterol deficient”:ab,ti OR RSH:ab,ti OR “Lethal Multiple Congenital Anomaly Syndrome”:ab,ti OR “Lethal Acrodysgenital”:ab,ti OR “7-Dehydrocholesterol Reductase”:ab,ti OR DHCR7:ab,ti OR “7 dehydrocholesterol delta 7 reductase”:ab,ti OR “3beta hydroxysterol delta 7 reductase”:ab,ti OR “NADPH-sterol delta 7-reductase”:ab,ti) AND (‘atorvastatin’/exp OR ‘bervastatin’/exp OR ‘cerivastatin’/exp OR ‘compactin’/exp OR ‘crilvastatin’/exp OR ‘dalvastatin’/exp OR ‘fluindostatin’/exp OR ‘glenvastatin’/exp OR ‘mevinolin’/exp OR ‘pitavastatin’/exp OR ‘pravastatin’/exp OR ‘rosuvastatin’/exp OR ‘simvastatin’/exp OR ‘tenivastatin’/exp OR Statin:ab,ti OR statins:ab,ti OR vastatin:ab,ti OR Atorvastatin*:ab,ti OR Liptonorm:ab,ti OR Lipitor:ab,ti OR atorlip:ab,ti OR aplactin:ab,ti OR atovarol:ab,ti OR glustar:ab,ti OR lowlipen:ab,ti OR sortis:ab,ti OR storvas:ab,ti OR tahor:ab,ti OR torvast:ab,ti OR zarator:ab,ti OR bervastatin:ab,ti OR cerivastatin:ab,ti OR crilvastatin:ab,ti OR dalvastatin:ab,ti OR fluvastatin*:ab,ti OR Fluvastatinum:ab,ti OR fluindostatin:ab,ti OR lescol:ab,ti OR canef:ab,ti OR cranoc:ab,ti OR lochol:ab,ti OR locol:ab,ti OR vastin:ab,ti OR glenvastatin:ab,ti OR lovastatin:ab,ti OR monacolin:ab,ti OR Mevinolin*:ab,ti OR Mevacor:ab,ti OR altocor:ab,ti OR altoprev:ab,ti OR artein:ab,ti OR belvas:ab,ti OR cholestra:ab,ti OR lipdip:ab,ti OR lipivas:ab,ti OR lostatin:ab,ti OR lovalip:ab,ti OR lovalord:ab,ti OR lovasterol:ab,ti OR lovastin:ab,ti OR lozutin:ab,ti OR mevinacor:ab,ti OR nergadan:ab,ti OR rodatin:ab,ti OR rovacor:ab,ti OR taucor:ab,ti OR meglutol:ab,ti OR mevastatin:ab,ti OR

Database/ Resource	Strategy
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ClinicalTrials.gov	SEARCH 1 Status: All studies Condition or disease: Lemli OR Opitz OR SLOS OR SLO OR RSH OR “cholesterol deficiency” OR “cholesterol deficient” OR “cholesterol deficiencies” OR “Lethal Multiple Congenital Anomaly Syndrome” OR “Lethal Acrodysgenital” SEARCH 2 Status: All studies Condition OR disease: “7 Dehydrocholesterol reductase” OR DHCR7 OR “7 dehydrocholesterol delta 7 reductase” OR “3beta hydroxysterol delta 7 reductase” OR “NADPH sterol delta 7 reductase”

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