Appendix C: Search strategies and review protocols

This guideline was developed in accordance with the process for short clinical guidelines set out in 'The guidelines manual' (2012). There is more information about how NICE clinical guidelines are developed on the NICE website.

C.1 Search strategies

The evidence reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in 'The guidelines manual' (2012). The aim of the systematic searches was to comprehensively identify the published evidence to answer the review questions developed by the Guideline Development Group and Internal Clinical Guidelines Technical Team.

The search strategies for the review questions were developed by the Information Services Team with advice from the Internal Clinical Guidelines Technical Team. Structured questions were developed using the PICO (population, intervention, comparison, outcome) model and translated into search strategies using subject heading and free text terms. The strategies were run across a number of databases,date restrictions were included when requested by the Technical Team

The NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched for economic evaluations. Search filters for economic evaluations and quality of life studies were used on bibliographic databases. Date restrictions were included when requested by the Technical Team.

Guideline Development Group members were also asked to alert the Internal Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

The searches were undertaken between July 2012 and June 2013 The re-run searches took place in June 2014.

C.2 Scoping searches

Scoping searches were undertaken in March 2012using the following websites and databases (listed in alphabetical order); browsing or simple search strategies were employed. The search results were used to provide information for scope development and project planning.

Guidance/guidelines

Department of Health

Canadian Medical Association Infobase

Guidelines International Network (GIN)

National Health and Research Council

New Zealand Guidelines Group

NHS Scotland

NICE Clinical Knowledge Summaries

NICE Evidence Services (previously NHS Evidence)

NICE Guidance

Professional bodies/associations/societies

Royal Colleges

Scottish Intercollegiate Guidelines Network (SIGN)

US National Guideline Clearing House

World Health Organization (WHO)

Systematic reviews/economic evaluations

Clinical Evidence

Cochrane Database of Systemic Reviews (CDSR)

Database of Abstracts of Reviews of Effects (DARE)

Health Technology Assessment Database (HTA)

National Institute for Health Research Health Technology assessment Programme

NHS R&D Service Delivery and Organisation Programme

Prospero

TRIP Database

NHS Economic Evaluation Database (NHS EED)

Health Economic Evaluations Database (HEED)

C3 Main searches

The following sources were searched for the topics presented in the sections below.

Cochrane Database of Systematic Reviews – CDSR (Wiley)

Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)

Database of Abstracts of Reviews of Effects – DARE (Wiley)

Health Technology Assessment Database – HTA (Wiley)

EMBASE (Ovid)

MEDLINE (Ovid)

MEDLINE In-Process (Ovid)

C4 Systematic reviews and mapping searches

The MEDLINE search strategies are presented below. They were translated for use in each of the other databases.

C.41 Review Question 1: Which pharmacological blood glucose lowering therapies should be used to control blood glucose levels in people with type 2 diabetes? July 2012

Ovid MEDLINE <1946 to July week 1 2012>

1 exp Diabetes Mellitus, Type 2/ (87707)

2 (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw. (75708)

3 ((Maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw. (2310)

4 ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw. (537)

5 ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw. (11408)

6 NIDDM.tw. (6762)

7 or/1-6 (113512)

8 Dipeptidyl-Peptidase IV Inhibitors/ (1767)

9 (Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw. (859)

10 (DPP* adj2 ("4" or "iv")).tw. (2738)

11 (Sitagliptin* or Januvia*).tw. (745)

12 (Vildagliptin* or Galvus*).tw. (443)

13 (Linagliptin* or Trajenta*).tw. (210)

14 (Saxagliptin* or Onglyza*).tw. (205)

15 Alogliptin*.tw. (116)

16 or/8-15 (3932)

17 Glucagon-Like Peptide 1/ (5464)

18 (Glucagon* adj Like adj Peptide adj "1").tw. (5553)

19 (GLP* adj "1").tw. (5577)

20 (Exenatide* or Byetta* or Bydureon*).tw. (1030)

21 (Liraglutide* or Victoza*).tw. (743)

22 (Lixisenatide* or Lyxumia*).tw. (24)

23 or/17-22 (8332)

24 Thiazolidinediones/ (9833)

25 (Thiazolidinedione* or Glitazone*).tw. (4900)

26 (Pioglitazone* or Actos*).tw. (3375)

27 or/24-26 (11936)

28 exp Sulfonylurea Compounds/tu [Therapeutic Use] (4680)

29 (Sulfonylurea* or Sulphonylurea*).tw. (7488)

30 Tolbutamide*.tw. (4050)

31 Glibenclamide*.tw. (6965)

32 (Glipizide* or Minodiab*).tw. (828)

33 (Glimepiride* or Amaryl*).tw. (1166)

34 (Gliclazide* or Diamicron*).tw. (945)

35 or/28-34 (19733)

36 Metformin/ (7273)

37 (Metformin* or Glucophage*).tw. (8503)

38 (Competact* or Janumet* or Eucreas*).tw. (11)

39 Biguanides/ (2768)

40 Biguanide*.tw. (2060)

41 or/36-40 (13057)

42 Acarbose/ (1088)

43 (Acarbose* or Glucobay*).tw. (1397)

44 or/42-43 (1588)

45 exp Insulins/tu [Therapeutic Use] (20286)

46 exp Insulin/ad [Administration & Dosage] (15892)

47 Insulin Infusion Systems/ (3982)

48 (Insulin* adj3 (treat* or therap* or administrat* or dos* or human* or analogue* or biphasic* or basal* or protamine* or isophane* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle*)).tw. (44593)

49 (Insulin* adj3 (Intermediate* or shortact* or short-act* or short act* or longact* or long-act* or long act* or ultralong* or ultra-long* or ultra long*)).tw. (1696)

50 (Actrapid* or Humulin* or Insuman* or Hypurin*).tw. (312)

51 (Aspart* or Novorapid*).tw. (76577)

52 (Glulisine* or Apidra*).tw. (187)

53 (Lispro* or Humalog*).tw. (854)

54 (Insulin* adj3 zinc* adj3 (suspension* or protamine*)).tw. (245)

55 (Detemir* or Levemir*).tw. (493)

56 (Glargine* or Lantus*).tw. (1342)

57 Degludec*.tw. (54)

58 (Isophane* or Insulatard* or Humulin* or Insuman* or Novomix*).tw. (331)

59 or/45-58 (140575)

60 Sodium-Glucose Transporter 2/ (326)

61 (Sodium* adj3 Glucose* adj3 Transporter* adj3 "2").tw. (104)

62 (Sodium* adj3 Glucose* adj3 (co-transporter* or cotransporter* or co transporter*) adj3 "2").tw. (183)

63 SGLT*.tw. (1264)

64 (Canagliflozin* or Dapagliflozin* or Empagliflozin*).tw. (125)

65 (Meglitinide* or Nateglinide* or Repaglinide*).tw. (894)

66 or/60-65 (2267)

67 16 or 23 or 27 or 35 or 41 or 44 or 59 or 66 (186449)

68 7 and 67 (25970)

69 Meta-Analysis.pt. (52213)

70 Meta-Analysis as Topic/ (14196)

71 Review.pt. (1924416)

72 exp Review Literature as Topic/ (7732)

73 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (60052)

74 (review$ or overview$).ti. (265955)

75 (systematic$ adj5 (review$ or overview$)).tw. (54185)

76 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4377)

77 ((studies or trial$) adj2 (review$ or overview$)).tw. (26148)

78 (integrat$ adj3 (research or review$ or literature)).tw. (5397)

79 (pool$ adj2 (analy$ or data)).tw. (14672)

80 (handsearch$ or (hand adj3 search$)).tw. (6759)

81 (manual$ adj3 search$).tw. (3235)

82 or/69-81 (2082990)

83 animals/ not humans/ (3974347)

84 82 not 83 (1946464)

85 Randomized Controlled Trial.pt. (390995)

86 Controlled Clinical Trial.pt. (90070)

87 Clinical Trial.pt. (505440)

88 exp Clinical Trials as Topic/ (297285)

89 Placebos/ (33814)

90 Random Allocation/ (81895)

91 Double-Blind Method/ (132149)

92 Single-Blind Method/ (19669)

93 Cross-Over Studies/ (36253)

94 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (762949)

95 (random$ adj3 allocat$).tw. (21255)

96 placebo$.tw. (162152)

97 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (129888)

98 (crossover$ or (cross adj over$)).tw. (59285)

99 or/85-98 (1423907)

100 animals/ not humans/ (3974347)

101 99 not 100 (1328812)

102 84 or 101 (3024023)

103 68 and 102 (12422)

C.4.2 Review Question 2: What are the serious adverse effects of long-term use of pharmacological interventions to control blood glucose in people with type 2 diabetes? January 2013

Ovid MEDLINE <1946 to January week 1 2013>

1 exp Diabetes Mellitus, Type 2/ (74370)

2 (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw. (61248)

3 ((Maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw. (2119)

4 ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw. (473)

5 ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw. (11155)

6 NIDDM.tw. (6633)

7 or/1-6 (95582)

8 Dipeptidyl-Peptidase IV Inhibitors/ (1158)

9 (Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw. (598)

10 (DPP* adj2 ("4" or "iv")).tw. (2100)

11 (Sitagliptin* or Januvia*).tw. (498)

12 (Vildagliptin* or Galvus*).tw. (314)

13 (Linagliptin* or Trajenta*).tw. (85)

14 (Saxagliptin* or Onglyza*).tw. (140)

15 Alogliptin*.tw. (79)

16 or/8-15 (2907)

17 Glucagon-Like Peptide 1/ (3812)

18 (Glucagon* adj Like adj Peptide adj "1").tw. (3838)

19 (GLP* adj "1").tw. (3809)

20 (Exenatide* or Byetta* or Bydureon*).tw. (670)

21 (Liraglutide* or Victoza*).tw. (350)

22 (Lixisenatide* or Lyxumia*).tw. (9)

23 or/17-22 (5794)

24 Thiazolidinediones/ (8371)

25 (Thiazolidinedione* or Glitazone*).tw. (4239)

26 (Pioglitazone* or Actos*).tw. (2761)

27 or/24-26 (10136)

28 exp Sulfonylurea Compounds/tu [Therapeutic Use] (4371)

29 (Sulfonylurea* or Sulphonylurea*).tw. (6700)

30 Tolbutamide*.tw. (3857)

31 Glibenclamide*.tw. (6282)

32 (Glipizide* or Minodiab*).tw. (777)

33 (Glimepiride* or Amaryl*).tw. (975)

34 (Gliclazide* or Diamicron*).tw. (862)

35 or/28-34 (17966)

36 Metformin/ (5951)

37 (Metformin* or Glucophage*).tw. (6856)

38 (Competact* or Janumet* or Eucreas*).tw. (11)

39 Biguanides/ (2625)

40 Biguanide*.tw. (1858)

41 or/36-40 (11027)

42 Acarbose/ (1033)

43 (Acarbose* or Glucobay*).tw. (1281)

44 or/42-43 (1465)

45 exp Insulins/tu [Therapeutic Use] (18814)

46 exp Insulin/ad [Administration & Dosage] (14523)

47 Insulin Infusion Systems/ (3585)

48 (Insulin* adj3 (treat* or therap* administrat* or dos* or human* or analogue* or biphasic* or basal* or protamine* or isophane* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle*)).tw. (40387)

49 (Insulin* adj3 (Intermediate* or shortact* or short-act* or short act* or longact* or long-act* or long act* or ultralong* or ultra-long* or ultra long*)).tw. (1521)

50 (Actrapid* or Humulin* or Insuman* or Hypurin*).tw. (296)

51 (Aspart* or Novorapid*).tw. (68526)

52 (Glulisine* or Apidra*).tw. (144)

53 (Lispro* or Humalog*).tw. (770)

54 (Insulin* adj3 zinc* adj3 (suspension* or protamine*)).tw. (239)

55 (Detemir* or Levemir*).tw. (400)

56 (Glargine* or Lantus*).tw. (1081)

57 Degludec*.tw. (19)

58 (Isophane* or Insulatard* or Humulin* or Insuman* or Novomix*).tw. (308)

59 or/45-58 (127084)

60 Sodium-Glucose Transporter 2/ (216)

61 (Sodium* adj3 Glucose* adj3 Transporter* adj3 "2").tw. (64)

62 (Sodium* adj3 Glucose* adj3 (co-transporter* or cotransporter* or co transporter*) adj3 "2").tw. (110)

63 SGLT*.tw. (1029)

64 (Canagliflozin* or Dapagliflozin* or Empagliflozin*).tw. (70)

65 (Meglitinide* or Nateglinide* or Repaglinide*).tw. (795)

66 or/60-65 (1885)

67 16 or 23 or 27 or 35 or 41 or 44 or 59 or 66 (165776)

68 7 and 67 (21837)

69 exp Cohort Studies/ (1211858)

70 (cohort adj (study or studies)).tw. (63699)

71 cohort analy$.tw. (2838)

72 (follow up adj (study or studies)).tw. (33378)

73 longitudinal.tw. (112432)

74 prospective.tw. (294067)

75 or/69-74 (1373943)

76 68 and 75 (2727)

77 Animals/ not Humans/ (3653831)

78 76 not 77 (2698)

79 limit 78 to english language (2446)

C.4.3 Review Question 3: What are the optimal target values for HbA1c, fasting blood glucose and post prandial blood glucose in people with type 2 diabetes? (December 2012)

Ovid MEDLINE <1946 to November week 3 2012>

1 exp Diabetes Mellitus, Type 2/ (76208)

2 (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw. (63336)

3 ((Maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw. (2166)

4 ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw. (475)

5 ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw. (11214)

6 NIDDM.tw. (6654)

7 or/1-6 (98196)

8 *Hemoglobin A, Glycosylated/ (5205)

9 (hemoglobin* adj3 glyc*).tw. (7213)

10 (haemoglobin* adj3 glyc*).tw. (3389)

11 glycohemoglobin*.tw. (633)

12 glycohaemoglobin*.tw. (97)

13 (hba1c or hb a1c).tw. (10948)

14 or/8-13 (21025)

15 *Fasting/ (7688)

16 fast*.tw. (291196)

17 (diet adj3 restrict*).tw. (3734)

18 *Postprandial Period/ (1828)

19 (postprandial* or post-prandial*).tw. (17493)

20 or/15-19 (305960)

21 *Blood Glucose/ (35609)

22 ((blood*or plasma* or serum*) adj3 (gluc* or sugar*)).tw. (13292)

23 or/21-22 (46815)

24 20 and 23 (11305)

25 14 or 24 (30758)

26 7 and 25 (12019)

27 Animals/ not Humans/ (3720385)

28 26 not 27 (11612)

29 limit 28 to english language (10446)

30 Epidemiologic Studies/ (5579)

31 exp Case-Control Studies/ (586243)
32 exp Cohort Studies/ (1234174)
33 Cross-Sectional Studies/ (150828)
34 Comparative Study.pt. (1621448)
35 case control$.tw. (65792)
36 case series.tw. (27324)
37 (cohort adj (study or studies)).tw. (65854)
38 cohort analy$.tw. (2895)
39 (follow up adj (study or studies)).tw. (33920)
40 (observational adj (study or studies)).tw. (33241)
41 longitudinal.tw. (115334)
42 prospective.tw. (299660)
43 retrospective.tw. (223737)
44 cross sectional.tw. (130903)
45 or/30-44 (3057909)
46 Meta-Analysis.pt. (37918)
47 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (45163)
48 (systematic$ adj4 (review$ or overview$)).tw. (40486)
49 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (3114)
50 ((studies or trial$) adj1 (review$ or overview$)).tw. (6564)
51 (integrat$ adj2 (research or review$ or literature)).tw. (3115)
52 (pool$ adj1 (analy$ or data)).tw. (7700)
53 (handsearch$ or (hand adj2 search$)).tw. (4489)
54 (manual$ adj2 search$).tw. (2443)
55 or/46-54 (100721)
56 animals/ not humans/ (3720385)
57 55 not 56 (98559)
58 Randomized Controlled Trial.pt. (342334)
59 Controlled Clinical Trial.pt. (85694)
60 Placebos/ (31583)
61 Random Allocation/ (76596)
62 Double-Blind Method/ (118498)
63 Single-Blind Method/ (17086)
64 Cross-Over Studies/ (30990)
65 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (570078)

66 (random$ adj2 allocat$).tw. (18136)

67 placebo$.tw. (141131)

68 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (116108)

69 (crossover$ or (cross adj over$)).tw. (52349)

70 or/58-69 (946027)

71 animals/ not humans/ (3720385)

72 70 not 71 (870899)

73 45 or 57 or 72 (3584205)

74 29 and 73 (6922)

C.4 Review Question 4: Should intensive or conventional target values be used to control blood glucose levels in people with type 2 diabetes? (January 2013)

Ovid MEDLINE <1946 to November week 4 2012>

1 exp Diabetes Mellitus, Type 2/ (76208)

2 (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw. (63336)

3 ((Maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw. (2166)

4 ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw. (475)

5 ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw. (11214)

6 NIDDM.tw. (6654)

7 or/1-6 (98196)

8 ((Intensiv* or aggressiv* or rigorous* or tight*) adj3 (glucose* or glycaemic* or glycemic*) adj3 (control* or lower*)).tw. (1734)

9 TGC.tw. (633)

10 (Intensiv* adj3 (strateg* or therap* or treat* or process* or protocol*)).tw. (20047)

11 or/8-10 (21994)

12 7 and 11 (1430)

13 Meta-Analysis.pt. (37918)

14 Meta-Analysis as Topic/ (12608)

15 Review.pt. (1758734)

16 exp Review Literature as Topic/ (6626)

17 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (45163)

18 (review$ or overview$).ti. (240815)

19 (systematic$ adj4 (review$ or overview$)).tw. (40486)

20 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (3114)

21 ((studies or trial$) adj1 (review$ or overview$)).tw. (6564)

22 (integrat$ adj2 (research or review$ or literature)).tw. (3115)

23 (pool$ adj1 (analy$ or data)).tw. (7700)

24 (handsearch$ or (hand adj2 search$)).tw. (4489)

25 (manual$ adj2 search$).tw. (2443)

26 or/13-25 (1896455)

27 animals/ not humans/ (3720385)

28 26 not 27 (1767418)

29 Randomized Controlled Trial.pt. (342334)

30 Controlled Clinical Trial.pt. (85694)

31 Clinical Trial.pt. (476450)

32 exp Clinical Trials as Topic/ (264416)

33 Placebos/ (31583)

34 Random Allocation/ (76596)

35 Double-Blind Method/ (118498)

36 Single-Blind Method/ (17086)

37 Cross-Over Studies/ (30990)

38 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (570078)

39 (random$ adj2 allocat$).tw. (18136)

40 placebo$.tw. (141131)

41 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (116108)

42 (crossover$ or (cross adj over$)).tw. (52349)

43 or/29-42 (1199393)

44 animals/ not humans/ (3720385)

45 43 not 44 (1121835)

46 28 or 45 (2686528)

47 12 and 46 (1011)

48 limit 47 to english language (858)

C.4.5 Review Question 5: Should self-monitoring be used to manage blood glucose levels in people with type 2 diabetes? (November 2012)

Ovid MEDLINE <1946 to November week 2 2012>

1 exp Diabetes Mellitus, Type 2/ (75950)

2 (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw. (63139)

3 ((Maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw. (2161)

4 ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw. (474)

5 ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw. (11209)

6 NIDDM.tw. (6651)

7 or/1-6 (97880)

8 Blood Glucose Self-Monitoring/ (3875)

9 ((Self-monitor* or self monitor* or home-monitor* or home monitor*) adj3 (glucose* or sugar* or blood* or urine* or glycaemi* or advice*)).tw. (1742)

10 ((Self-test* or self test* or home-test* or home test*) adj3 (glucose* or sugar* or blood* or urine* or glycaemi* or advice*)).tw. (62)

11 ((Self-assess* or self assess* or home-assess* or home assess*) adj3 (glucose* or sugar* or blood* or urine* or glycaemi* or advice*)).tw. (36)

12 ((Self-manag* or self manage* or home-manage* or home manage*) adj3 (glucose* or sugar* or blood* or urine* or glycaemi* or advice*)).tw. (93)

13 ((Self-control* or self control* or home-control* or home control*) adj3 (glucose* or sugar* or blood* or urine* or glycaemi* or advice*)).tw. (64)

14 SMBG.tw. (478)

15 (Fingerprick* or fingerstick*).tw. (456)

16 ((Finger* or thumb*) adj3 (prick* or stick*)).tw. (883)

17 (Blood adj3 glucose* adj3 meter*).tw. (371)

18 or/8-17 (6300)

19 7 and 18 (1464)

20 limit 19 to (ed=20070101-20121115 and english language) (712)

21 Randomized Controlled Trial.pt. (341859)

22 Controlled Clinical Trial.pt. (85658)

23 Clinical Trial.pt. (476183)

24 exp Clinical Trials as Topic/ (264107)

25 Placebos/ (31561)

26 Random Allocation/ (76545)

27 Double-Blind Method/ (118375)

28 Single-Blind Method/ (17053)

29 Cross-Over Studies/ (30947)

30 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (569143)

31 (random$ adj2 allocat$).tw. (18118)

32 placebo$.tw. (140976)

33 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (116001)

34 (crossover$ or (cross adj over$)).tw. (52292)

35 or/21-34 (1197753)

36 animals/ not humans/ (3717557)

37 35 not 36 (1120276)

38 Meta-Analysis.pt. (37760)

39 Meta-Analysis as Topic/ (12581)

40 Review.pt. (1756044)

41 exp Review Literature as Topic/ (6611)

42 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (44982)

43 (review$ or overview$).ti. (240422)

44 (systematic$ adj4 (review$ or overview$)).tw. (40325)

45 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (3103)

46 ((studies or trial$) adj1 (review$ or overview$)).tw. (6551)

47 (integrat$ adj2 (research or review$ or literature)).tw. (3106)

48 (pool$ adj1 (analy$ or data)).tw. (7671)

49 (handsearch$ or (hand adj2 search$)).tw. (4482)

50 (manual$ adj2 search$).tw. (2443)

51 or/38-50 (1893544)

52 animals/ not humans/ (3717557)

53 51 not 52 (1764589)

54 37 or 53 (2682475)

55 20 and 54 (348)

C.46 Review Question 6: Should aspirin and/ or clopidogrel be used for primary prevention of cardiovascular disease in people with type 2 diabetes? (November 2012)

Ovid MEDLINE <1946 to October week 4 2012>

1 exp Diabetes Mellitus, Type 2/ (75451)

2 (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw. (62632)

3 ((Maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw. (2152)

4 ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw. (474)

5 ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw. (11204)

6 NIDDM.tw. (6648)
7 or/1-6 (97234)
8 Aspirin/ (36490)
9 (Aspirin* or acetylsalicylic acid* or micropirin* or caprin*).tw. (41115)
10 (Clopidogrel* or Plavix* or Grepid*).tw. (5905)
11 or/8-10 (56239)
12 7 and 11 (658)
13 Animals/ not Humans/ (3707435)
14 12 not 13 (639)
15 limit 14 to (ed=20070101-20121107 and english language) (301)
16 Meta-Analysis.pt. (37222)
17 Meta-Analysis as Topic/ (12516)
18 Review.pt. (1749326)
19 exp Review Literature as Topic/ (6580)
20 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (44398)
21 (review$ or overview$).ti. (239135)
22 (systematic$ adj4 (review$ or overview$)).tw. (39724)
23 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (3074)
24 ((studies or trial$) adj1 (review$ or overview$)).tw. (6497)
25 (integrat$ adj2 (research or review$ or literature)).tw. (3081)
26 (pool$ adj1 (analy$ or data)).tw. (7594)
27 (handsearch$ or (hand adj2 search$)).tw. (4445)
28 (manual$ adj2 search$).tw. (2423)
29 or/16-28 (1886158)
30 animals/ not humans/ (3707435)
31 29 not 30 (1757509)
32 Randomized Controlled Trial.pt. (340101)
33 Controlled Clinical Trial.pt. (85462)
34 Clinical Trial.pt. (475088)
35 exp Clinical Trials as Topic/ (262887)
36 Placebos/ (31496)
37 Random Allocation/ (76290)
38 Double-Blind Method/ (117930)

39 Single-Blind Method/ (16934)

40 Cross-Over Studies/ (30793)

41 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (565398)

42 (random$ adj2 allocat$).tw. (18044)

43 placebo$.tw. (140317)

44 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (115572)

45 (crossover$ or (cross adj over$)).tw. (52021)

46 or/32-45 (1191602)

47 animals/ not humans/ (3707435)

48 46 not 47 (1114558)

49 31 or 48 (2671072)

50 15 and 49 (145)

C.4.7 Review Question 7: What pharmacological treatment should be used to manage erectile dysfunction in men with type 2 diabetes? (October 2012 [multi-file search strategy])

Ovid MEDLINE <1946 to October week 1 2012>

Ovid MEDLINE-in-Process <October 10, 2012>

EMBASE (Ovid) <1980 to 2012 week 40>

1 exp Diabetes Mellitus, Type 2/ use mesz (75110)

2 exp non insulin dependent diabetes mellitus/ use emez (116377)

3 (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw. (161562)

4 ((Maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw. (4594)

5 ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw. (1121)

6 ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw. (24574)

7 NIDDM.tw. (14551)

8 Diabetes Mellitus, Type 1/ use mesz (57276)

9 exp insulin dependent diabetes mellitus/ use emez (70113)

10 (Type* adj3 ("1" or "I" or one*) adj3 (diabete* or diabetic*)).tw. (77647)

11 ((Autoimmune* or auto-immune* or auto immune* or sudden-onset* or sudden onset* or brittle* or juvenile-onset* or juvenile onset*) adj3 (diabete* or diabetic*)).tw. (9587)

12 ((Ketosis-prone* or ketosis prone*) adj3 (diabete* or diabetic*)).tw. (221)

13 (Insulin* adj3 depend* adj3 (diabete* or diabetic*)).tw. (54382)

14 IDDM.tw. (14280)

15 or/1-14 (368668)

16 exp Erectile Dysfunction/ use mesz (14699)

17 exp erectile dysfunction/ use emez (15908)

18 impotence/ use emez (13770)

19 ((Erectile* or sex*) adj3 dysfunct*).tw. (37450)

20 ED.tw. (71486)

21 Impotence*.tw. (11497)

22 or/16-21 (126086)

23 Testosterone/ use mesz (57123)

24 testosterone/ use emez (75502)

25 testosterone undecanoate/ use emez (1362)

26 Testosterone*.tw. (124639)

27 (Restandol Testocaps or Striant SR or Nebido or Sustanon or Virormone or Intrinsa or Testim or Testogel or Tostran).tw. (843)

28 TRT.tw. (1696)

29 or/23-28 (170672)

30 Prostaglandins E/ use mesz (14417)

31 Alprostadil/ use mesz (6451)

32 prostaglandin E1/ use emez (14587)

33 Prostaglandin* E.tw. (13009)

34 (pge1 or pge-1 or "pge 1" or "pg e1" or "pg e-1" or "pg e 1").tw. (12625)

35 (Alprostadil* or Caverject* or Viridal* or Muse).tw. (1923)

36 or/30-35 (49004)

37 Phosphodiesterase 5 Inhibitors/ use mesz (997)

38 phosphodiesterase V inhibitor/ use emez (4034)

39 "Phosphodiesterase* 5 Inhibitor*".tw. (1761)

40 "Phosphodiesterase* V Inhibitor*".tw. (95)

41 ((pde5 or pde-5 or "pde 5") adj3 Inhibitor*).tw. (3661)

42 ((pdeV or pde-V or "pde V") adj3 Inhibitor*).tw. (130)

43 sildenafil/ use emez (13334)

44 tadalafil/ use emez (3345)

45 vardenafil/ use emez (2597)

46 (Sildenafil or Viagra or Revatio or Tadalafil or Cialis or Vardenafil or Levitra).tw. (14903)

47 or/37-46 (23696)

48 limit 47 to ed=20070101-20121011 use mesz [Limit not valid in Embase; records were retained] (3201)

49 limit 47 to em=200700-201240 use emez [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained] (9857)

50 48 or 49 (13058)

51 29 or 36 or 50 (230891)

52 15 and 22 and 51 (538)

53 Animals/ not Humans/ use mesz (5497586)

54 Nonhuman/ not Human/ use emez (3176971)

55 53 or 54 (8660434)

56 52 not 55 (517)

57 limit 56 to english language (466)

58 remove duplicates from 57 (356)

C.5 Health economics searches

The following sources were searched to identify economic evaluations and quality of life data featuring the patient population of type 2 diabetes

Ovid MEDLINE

Ovid MEDLINE-in-Process

EMBASE (Ovid)

NHS EED (Wiley)

HEED

The following search filters were added to all clinical search strategies:

1 Economics/ (26636)

2 exp "Costs and Cost Analysis"/ (172722)

3 Economics, Dental/ (1861)

4 exp Economics, Hospital/ (18697)

5 exp Economics, Medical/ (13342)

6 Economics, Nursing/ (3871)

7 Economics, Pharmaceutical/ (2445)

8 Budgets/ (9411)

9 exp Models, Economic/ (9415)

10 Markov Chains/ (9010)

11 Monte Carlo Method/ (18608)

12 Decision Trees/ (8471)

13 econom$.tw. (143763)

14 cba.tw. (8570)

15 cea.tw. (15284)

16 cua.tw. (736)

17 markov$.tw. (10445)

18 (monte adj carlo).tw. (19126)

19 (decision adj2 (tree$ or analys$)).tw. (7051)

20 (cost or costs or costing$ or costly or costed).tw. (280831)

21 (price$ or pricing$).tw. (21406)

22 budget$.tw. (16270)

23 expenditure$.tw. (32597)

24 (value adj2 (money or monetary)).tw. (1121)

25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3114)

26 or/1-25 (607987)

27 "Quality of Life"/ (108608)

28 quality of life.tw. (123243)

29 "Value of Life"/ (5320)

30 Quality-Adjusted Life Years/ (6276)

31 quality adjusted life.tw. (5117)

32 (qaly$ or qald$ or qale$ or qtime$).tw. (4282)

33 disability adjusted life.tw. (995)

34 daly$.tw. (992)

35 Health Status Indicators/ (19253)

36 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (13766)

37 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (936)

38 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2220)

39 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (18)

40 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (319)

41 (euroqol or euro qol or eq5d or eq 5d).tw. (3108)

42 (qol or hql or hqol or hrqol).tw. (21283)

43 (hye or hyes).tw. (51)

44 health$ year$ equivalent$.tw. (36)

45 utilit$.tw. (101718)

46 (hui or hui1 or hui2 or hui3).tw. (775)

47 disutili$.tw. (179)

48 rosser.tw. (69)

49 quality of wellbeing.tw. (5)

50 quality of well-being.tw. (314)

51 qwb.tw. (153)

52 willingness to pay.tw. (1858)

53 standard gamble$.tw. (615)

54 time trade off.tw. (670)

55 time tradeoff.tw. (194)

56 tto.tw. (523)

57 or/27-56 (289501)

58 26 or 57 (858294)

C.5.1.1 Review question 1: Which pharmacological blood glucose lowering therapies should be used to control blood glucose levels in people with type 2 diabetes?

	Details	Additional Comments	Status
Review question 1	Which pharmacological blood glucose-lowering therapies should be used initially to control blood glucose levels in people with type 2 diabetes? When first intensification of treatment is indicated, which blood glucose lowering therapies should be used to control blood glucose levels? When second intensification of treatment is indicated, which blood glucose lowering therapies should be used to control blood glucose levels? When third intensification of treatment is indicated, which blood glucose lowering therapies should be used to control blood glucose levels?	See objectives for further details of specific drug comparisons within initial therapy and further intensification	Following GDG meeting 6, the structure and wording of this review question changed to refer to initial therapy, followed by first, second and third intensification of pharmacological therapy (replacing monotherapy, dual therapy and triple therapy)
Objectives	**All anti diabetic treatments:** • Which drugs should be used as part of initial therapy and further intensification as blood glucose control declines? • Should blood glucose-lowering therapies be used by all people with type 2 diabetes or should this be restricted to specific sub-groups of the population? When should alternative drugs be considered? • What adverse events and/or safety concerns are associated with pharmacological interventions? • When different formulations of the same therapy are available (i.e. extended release vs. conventional), which one should be used?		During the development of the guideline, the insulin specific objectives were replaced with specific drug comparisons that were prioritised by the GDG at meeting 6 (NB: OAD relates to non-insulin anti diabetics and includes GLP-1s which are injected) : **initial therapy** 1 OAD vs. 1 OAD 1 OAD vs. placebo **First intensification** 2 NIT vs. 2 NIT **Second intensification** 3 NIT vs. 3 NIT Insulin + 2 NIT vs. 3 NIT Insulin + 1 NIT vs. 3 NIT

	Details	Additional Comments	Status
			Insulin + 1 NIT vs. insulin + 1 NIT Insulin + 2 NIT vs. insulin + 2 NIT Insulin vs. 3 NIT Insulin vs. insulin + 2 NIT Insulin vs. insulin + 1 NIT Insulin + 1 NIT vs. insulin + 2 NIT **Third intensification** 3 NIT vs. 4 NITs *OAD oral antidiabetic drug* *NIT non-insulin based therapies*
Language	English		
Study design	RCTs and systematic reviews	For cross over trials, a 4-6 week washout period was considered appropriate. The following decisions about data extraction for cross over trials were taken: • If the trial reports analysis that is appropriate for cross-over trials and a washout period of 4-6 weeks then the end of treatment data will be extracted • If the trial reports analysis that is appropriate for cross-over trials but a washout period <4 weeks then data from the first treatment period will be extracted • If the trial does not report analysis that is appropriate for cross-over trials then data from the first treatment	

	Details	Additional Comments	Status
		period will be extracted	
Status	Published papers (full papers only)		
Population	Adults (aged 18 years and over) diagnosed with type 2 diabetes. Specific patient sub-groups for whom the management of type 2 diabetes may vary, this may include but is not restricted to: •Older adults •People with renal impairment •People in specific ethnic groups •People in specific cardiovascular risk groups		
Interventions	Pharmacological management of blood glucose levels. The following blood glucose-lowering therapies will be examined as part of treatment strategies involving initial therapy followed by first, second and third intensification : • DPP-4 inhibitors: ○ sitagliptin, vildagliptin, linagliptin and saxagliptin • glucagon-like peptide-1 (GLP-1) receptor agonists: ○ exenatide (conventional formula and prolonged release), liraglutide and lixisenatide • thiazolidinediones (peroxisome proliferator-activated receptor gamma [PPAR-γ] agonists): ○ pioglitazone • sulfonylureas • metformin • insulin • acarbose	**Additional search terms for update**: Sulphonylureas (Glibenclamide, Gliclazide, Glimepiride, Glipizide, Tolbutamide), Insulin, Acarbose (alpha glucosidase inhibitor) **Previous search terms used in CG87:** Glucagon-Like Peptide 1 or GLP-1, dipeptidyl peptidase-4 inhibitor, dipeptidyl peptidase-IV inhibitor, dpp-iv inhibitor, dpp-4 inhibitor, glargine or detemir (for insulin searches)	

	Details	Additional Comments	Status
	• meglitinides		
Comparator	As specified in individually listed comparisons		
Outcomes	Changes in blood glucose levels (HbA1c) Changes in weight or Body Mass Index (BMI) Frequency, severity and timing of hypoglycaemic episodes Adverse events The development of microvascular and macrovascular complications: • retinopathy (specific lesions or macular changes, referable retinopathy, blindness/loss of vision, visual acuity) • kidney damage (eGFR, serum creatinine, proteinuria, microalbuminuria, dialysis) • cardiovascular disease (myocardial infarction, heart failure, stroke, ACS, TIA, revascularisation and stenting) • foot complications (amputations, diabetic foot ulcers, charcot osteoarthropathy, diabetic foot infection) Changes in lipid levels (LDL-C, HDL-C, TG and TC) and blood pressure Mortality Health-related quality of life Resource use and cost Progression to insulin treatment Total daily dose of insulin (where insulin treatment has been used)	**CG66 and CG87:** Progression to insulin treatment also considered as outcome for GLP-1's and total daily dose of insulin when assessing insulin as treatment (alone or in combination). Cardiovascular risk factors were also reported (i.e. lipid, blood pressure data etc.)	At GDG 6, the group agreed that the important blood glucose measures for this review question was HbA1c as these are commonly used in clinical practice. Fasting and postprandial blood glucose are not normally used and for postprandial levels, there is no standardised method for assessment and self-monitored levels were also not important as more accurate measures of blood glucose levels were available. The GDG also agreed that beta-cell function and insulin resistance are not used in clinical practice and should not be reported. In addition, markers for CVD risk such as oxidative stress and c-peptides are also excluded. The GDG discussed potential effect modifiers and suggested that the main variables were age, weight, renal function, duration of diabetes, activity levels, baseline HbA1c, diet and ethnicity. The minimal important difference (MID) for HbA1c was agreed to be 0.5%. For blood pressure this was 5 mmHg, BMI was 10%, LDL cholesterol was 1mmol and 50 units for total daily insulin use. All other binary outcomes were 25% and for

	Details	Additional Comments	Status
			continuous outcomes any statistically significant findings were considered clinically important. **Critical outcomes:** • change in BG levels (HbA1c) • hypoglycaemia and • adverse events **Important outcomes:** • change in weight •
Other criteria for inclusion/ exclusion of studies	**Inclusion criteria used in CG87:** • For RCTs, treatment for a minimum of 12 weeks (because of the time it takes for glycaemic control to be reflected in HbA1c, but this should be regarded as the minimum acceptable rather than satisfactory. Longer duration studies would be better) • For systematic reviews, they should include at least one RCT of at least 12 weeks duration (trials of at least 24 weeks' duration are preferred) • Standard UK practice as comparator (CG66 used for each drug). This criterion was not applied in the update **Additional inclusion for update:** • Open label trials • Trials examining head-to-head drug comparisons • For first and second intensification, trials which do not report dosing information were included (this is because patients are most likely to be on pre-existing therapy, which has been titrated to the tolerated dose before starting the study	For the update, the use of standard UK comparators was not used as an inclusion criterion and all licensed drug comparisons were explored. Systematic reviews were only used as a source of reference.	Data from the following time points were extracted: • 3 months (12-16 weeks) • 6 months (22-30 weeks) • 12 months (44-60 weeks) • 24 months (96-112 weeks)

	Details	Additional Comments	Status
	drug(s). Therefore specific dosing is less important) **Exclusion criteria used in CG87:** • Comparison with unlicensed indications (e.g. this includes NPL insulin; ILPS insulin; monotherapy with either GLP-1s or nateglinide) **Additional exclusion criteria for update:** • Studies examining a mixed population of people with type 1 and 2 diabetes (unless subgroup analyses are reported or 85% or more of the study population have type 2 diabetes) • Non-randomised evidence (including cohort studies, case–control studies and case series, uncontrolled or single arm trials), narrative reviews, conference abstracts, letters and editorials, observational study, trial protocols etc. • Comparisons with drugs not listed in scope (e.g. this includes rosiglitazone, see scope for more details) • Not focusing on pharmacological management of blood glucose levels in people with type 2 diabetes • Trials focusing on markers of CVD or other diabetic complications without any blood glucose measures • Trials of monotherapy using only doses of blood glucose-lowering therapies above the recommended daily dose • Mode of delivery that is not licensed (e.g. inhaled insulin) • Drug comparison not of interest (e.g. this includes comparisons across treatment strategy, see objectives for more details)		

	Details	Additional Comments	Status
	• Unclear washout of previous pharmacological treatment or proportion or all patients continued pre-existing or other OADs (papers were excluded unless this represented a small proportion of patients <5%) • Unclear if analyses were adjusted in trials where rescue medication was available • For initial therapy, trials were excluded if there was no information relating to doses (this is because patients are generally drug naïve and so it is important to establish that starting doses in trials are within the licensed recommendations) • Trials termed monotherapy with individuals who were not drug naïve or had washout periods ≤4 weeks • Other methodological reasons (e.g. no explicit inclusion/exclusion criteria)		
Previous search strategies	**Previous date restrictions for CG87:** GLP-1's limited from 1990-April 2008 DPP-4 inhibitors limited from 1996-April 2008 Insulin (glargine and detemir) limited from 1996-April 2008 Thiazolidinediones limited from 1996-January 2008 (week 18 for safety and EMBASE) **Previous date restrictions for CG66:** Metformin limited from 2001-2007 Sulphonylurea limited from 2001-2007 Acarbose limited from 2001-2007 Biphasic insulin preparations (vs. NPH or biphasic analogue preparations) limited from 2001-2007 Multiple analogue insulin injections limited	Full search for GLP-1 agonists and DPP-4 inhibitors did not have a date restriction applied as some of the individual drugs within these classes have not been previously searched for	

	Details	Additional Comments	Status
	from 2001-2007 Methods of insulin delivery 1995-2007 Drugs not covered by previous searches: DPP-4 inhibitors linagliptin and alogliptin GLP-1 mimetic lixisenatide		
Search strategies for update	RCTs and systematic reviews. Each drug class can have a date restriction for searches (see above for details of previous searches). **Drugs reviewed in CG87:** GLP-1 or exenatide or liraglutide (April 2008-present) DPP-4 or vildagliptin or sitagliptin or saxagliptin (April 2008-present) Insulin glargine or insulin detemir (April 2008-present) Thiazolidinediones pioglitazone (January 2008-present) **Drugs reviewed in CG66 only:** Metformin (2007-present) Sulphonylureas (2007-present) Acarbose (2007-present) Insulin (2007-present) **Drugs not reviewed in either CG66 or CG87:** DPP-4 inhibitors linagliptin and alogliptin (no date restriction) GLP-1 mimetic lixisenatide (no date restriction)	NB: In CG87 Ovid Auto-alerts were set-up for the clinical effectiveness for the rest of 2008 in order to retrieve new studies published after the initial searches were run.	
Review strategies	The NICE methodology checklist for RCTs and systematic reviews will be used as a guide to appraise the quality of individual studies Data on all included studies will be extracted into evidence tables.		

	Details	Additional Comments	Status
	Where statistically possible, a meta-analytical approach or mixed treatment comparison (MTC) will be used All key outcomes from the evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. Outcomes from previously included studies will be incorporated into the analysis and GRADE profiles where appropriate.		
Identified key studies	N/A		

<Insert Note here>

C.5.1.2 Review question 2: What are the serious adverse effects of long-term use of pharmacological interventions to control blood glucose in people with type 2 diabetes?

	Details	Additional comments	Status
Review question 2	What are the serious adverse effects of long-term use of pharmacological interventions to control blood glucose in people with type 2 diabetes?		

Objectives	What long term serious adverse effects are associated with the use of the following pharmacological blood glucose-lowering therapies (either alone or in combination):
	• DPP-4 inhibitors:
	  ○ sitagliptin, vildagliptin, linagliptin and saxagliptin
	• glucagon-like peptide-1 (GLP-1) receptor agonists:
	  ○ exenatide (conventional formula and prolonged release), liraglutide and lixisenatide
	• thiazolidinediones (peroxisome proliferator-activated receptor gamma [PPAR-γ] agonists):
	  ○ pioglitazone
	• sulfonylureas
	• metformin
	• insulin		

	Details	Additional comments	Status
	• acarbose • meglitinides Are adverse events and microvascular and macrovascular complications more likely to occur in specific subgroups of the population?		
Language	English		
Study design	Prospective cohort studies (including open label continuation studies)		
Status	Published papers (full papers only)		At GDG 1 the group discussed that this question may overlap with the aims of MHRA who may also use unpublished data. However, it was agreed that this review question will also cover safety issues when blood glucose-lowering therapies are compared with each other. This has been restricted to published papers only
Population	Adults (aged 18 years and over) diagnosed with type 2 diabetes. Specific patient sub-groups for whom the management of type 2 diabetes may vary, this may include but is not restricted to: • Older adults • People with renal impairment • People in specific ethnic groups • People in specific cardiovascular risk groups		
Intervention	The following blood glucose-lowering therapies will be examined as part of treatment strategies involving monotherapy, dual therapy and triple therapy: • DPP-4 inhibitors: ○ sitagliptin, vildagliptin, linagliptin and saxagliptin • glucagon-like peptide-1 (GLP-1) receptor agonists: ○ exenatide (conventional formula and prolonged release), liraglutide and lixisenatide	Previous search terms (CG87): risk or safety or adverse or harm or pharmacovigilance, side-effect or precaution or warning or	

	Details	Additional comments	Status
	• thiazolidinediones (peroxisome proliferator-activated receptor gamma [PPAR-γ] agonists): ○ pioglitazone • sulfonylureas • metformin • insulin • acarbose • meglitinides	contraindication or contra-indication	
Comparator	placebo/no treatment or other treatment (including combinations)		
Outcomes	• cancer • cardiovascular disease (myocardial infarction, heart failure, stroke, ACS, TIA, revascularisation and stenting) • cognitive impairment • fracture • pancreatic disease • morbidity • mortality		
Other criteria for inclusion/exclusion of studies	**Include:** • Studies with a minimum sample size of 200 • Studies with follow-up of at least 2 years • Studies focusing on the development of long-term safety issues such as renal failure, severe pancreatitis, cancer (thyroid, bladder etc), cardiac failure and other microvascular or macrovascular complications. **Exclude:** • Conference abstracts, letters, editorials and other non-prospective observational studies (evidence from registries and healthcare databases are considered to be retrospective) • Studies that do not report the incidence of the safety issue or exposure to pharmacological treatment • Studies examining a mixed population of people with type 1 and 2 diabetes (unless subgroup analyses are reported or ≥85% of the study		At GDG 1 the group agreed that studies with a minimum of 200 people with diabetes should be included. The GDG agreed that a minimum 2 year follow-up would be sufficient to allow for adverse events and complications to occur (shorter durations will be covered by review question 1)

	Details	Additional comments	Status
	population have type 2 diabetes)		
Search strategies	prospective cohort studies. No date restriction.		
Review strategies	The NICE methodology checklist for observational studies will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytical approach will be used to give an overall summary effect. All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. Outcomes from previously included studies will be incorporated into the analysis and GRADE profiles where appropriate. Sub-group analysis will be undertaken where appropriate.		
Identified key studies	N/A		

C.5.1.3 Review question 3: What are the optimal target values for HbA1c, fasting blood glucose and post prandial blood glucose in people with type 2 diabetes?

	Details	Additional comments	Status
Review question 3	What are the optimal target values for HbA1c, fasting blood glucose and post-prandial blood glucose in people with type 2 diabetes?		
Objectives	• What blood glucose values should be targeted to minimise the risk of future vascular damage? • Do optimal target values for blood glucose measures differ according to pharmacological treatment and specific subgroups of the population?		
Language	English		
Study design	prospective cohort studies		
Status	Published papers (full papers only)		
Population	Adults (aged 18 years and over) diagnosed with type 2 diabetes. Specific patient sub-groups for whom the management of type 2 diabetes may vary, this may include but is not restricted to: • Older adults		

	Details	Additional comments	Status
	• People with renal impairment • People in specific ethnic groups • People in specific cardiovascular risk groups		
Intervention	N/A	Search terms: N/A	
Comparator	N/A		
Outcomes	The development of microvascular and macrovascular complications • retinopathy (specific lesions or macular changes, referable retinopathy, blindness/loss of vision, visual acuity) • kidney damage (eGFR, serum creatinine, proteinuria, microalbuminuria, dialysis) • cardiovascular disease (myocardial infarction, heart failure, stroke, ACS, TIA, revascularisation and stenting) • foot complications (amputations, diabetic foot ulcers, charcot osteoarthropathy, diabetic foot infection) Mortality		
Other criteria for inclusion/exclusion of studies	**Include:** • Prospective observational cohort studies focusing on the development of microvascular or macrovascular complications and its association with blood glucose measures **Exclude:** • Studies focusing on an association between HbA1c and microvascular or macrovascular complications without giving further information about the association • Studies focusing only on an association between the variability of blood glucose measures (e.g. HbA1c-CV, HbA1c-SD) and long-term complications • Case series, conference abstracts, letters and editorials and other non-prospective observational studies • Studies examining a mixed population of people with type 1 and 2 diabetes (unless subgroup analyses are reported) • Exploratory prognostic studies which examine HbA1c as one of many risk factors for diabetic complications • Studies including rosiglitazone	NB: due to the large UKPDS study in CG66 studies published from 2001 onwards were only considered if there was a sample size N of at least 2000 people with type 2 or mixed population of type 1 and 2 diabetes. Studies were not reviewed if they simply found associations between HbA1c and complications without giving further information	At GDG 1, the group discussed the sample size threshold that was used in the previous guideline and agreed this was arbitrary and may need to be lower for specific sub-groups of the population (this exclusion criteria was removed for the update). It was also agreed that for this review question, including papers with the majority of people with type 2 diabetes may not be appropriate as small numbers of people with type 1 diabetes may bias the findings. Studies on rosiglitazone

	Details	Additional comments	Status
			are to be excluded as its association with cardiovascular mortality is likely to confound the review findings.
Search strategies	Observational study design. No date restriction on all blood glucose should be applied as the sample size threshold in CG66 for HbA1c studies was removed		
Review strategies	Appropriate NICE methodology checklists (depending on the study design) will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytical approach will be used to give an overall summary effect. All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. Outcomes from previously included studies will be incorporated into the analysis and GRADE profiles where appropriate. Sub-group analysis will be undertaken when appropriate		
Identified key studies	N/A		

C.5.1.4 Review question 4: Should intensive or conventional target values be used to control blood glucose levels in people with type 2 diabetes?

	Details	Additional comments	Status
Review question 4	Should intensive or conventional target values be used to control blood glucose levels in people with type 2 diabetes?		
Objectives	• Should intensive strategies that target HbA1c levels, fasting blood glucose and post-prandial blood glucose below conventional values be used to manage blood glucose levels in people with type 2 diabetes? • Should intensive strategies be used by all people with type 2 diabetes or should this be restricted to specific sub-groups of the population? • When should intensive strategies be used to manage blood glucose levels in people with type 2 diabetes?		
Language	English		

	Details	Additional comments	Status
Study design	RCT's and systematic reviews		
Status	Published papers (full papers only)		
Population	Adults (aged 18 years and over) diagnosed with type 2 diabetes. Specific patient sub-groups for whom the management of type 2 diabetes may vary, this may include but is not restricted to: • Older adults • People with renal impairment • People in specific ethnic groups • People in specific cardiovascular risk groups		

Intervention	Intensive blood glucose control (using pharmacological blood glucose-lowering therapies listed below) with target blood glucose levels lower than conventional values:
	• DPP-4 inhibitors:
	• sitagliptin, vildagliptin, linagliptin and saxagliptin
	• glucagon-like peptide-1 (GLP-1) receptor agonists:
	  ○ exenatide (conventional formula and prolonged release), liraglutide and lixisenatide
	• thiazolidinediones (peroxisome proliferator-activated receptor gamma [PPAR-γ] agonists):
	  ○ pioglitazone
	• sulfonylureas
	• metformin
	• insulin
	• acarbose
	• meglitinides		

Comparator	Conventional/standard blood glucose targets		
Outcomes	Changes in weight or Body Mass Index (BMI) Frequency, severity and timing of hypoglycaemic episodes The development of microvascular and macrovascular complications • retinopathy (specific lesions or macular changes, referable retinopathy, blindness/loss of vision, visual acuity) • kidney damage (eGFR, serum creatinine, proteinuria, microalbuminuria,		

	Details	Additional comments	Status
	dialysis) • cardiovascular disease (myocardial infarction, heart failure, stroke, ACS, TIA, revascularisation and stenting) • foot complications (amputations, diabetic foot ulcers, charcot osteoarthropathy, diabetic foot infection) Mortality		
Other criteria for inclusion/exclusion of studies	**Include:** • RCTs focusing on the use of intensive vs. conventional blood glucose control (this includes multifactorial interventions that include intensive HbA1c or other blood glucose targets and intensive insulin therapy) **Exclude:** • Non-randomised evidence (including cohort studies, case–control studies and case series), narrative reviews, conference abstracts, letters and editorials • Studies examining a mixed population of people with type 1 and 2 diabetes (unless subgroup analyses are reported)		It was agreed at GDG 1 that for this review question, including papers with the majority of people with type 2 diabetes may not be appropriate as small numbers of people with type 1 diabetes may bias the findings.
Search strategies	RCT and systematic review filter. No date restriction.		
Review strategies	Appropriate NICE methodology checklists (depending on the study design) will be used as a guide to appraise the quality of individual studies Data on all included studies will be extracted into evidence tables Where statistically possible, a meta-analytical approach will be used to give an overall summary effect All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. Outcomes from previously included studies will be incorporated into the analysis and GRADE profiles where appropriate. Sub-group analysis will be undertaken when appropriate		
Identified key studies	N/A		

C.5.1.5 Review question 5: Should self-monitoring be used to manage blood glucose levels in people with type 2 diabetes?

	Details	Additional comments	Status
Review question 5	Should self-monitoring be used to manage blood glucose levels in people with type 2 diabetes?		This review question was amended at GDG 1 to

	Details	Additional comments	Status
			cover the use of self-monitoring in people treated with lifestyle intervention alone
Objectives	Should self-monitoring be used to manage blood glucose levels in people with type 2 diabetes? This will include: • people taking any glucose-lowering therapies (alone or in combination) • people receiving lifestyle intervention alone (without glucose-lowering therapies) Should all people with type 2 diabetes use self-monitoring or should this be restricted to specific sub-groups of the population? What target values should people who self-monitor blood glucose levels aim for? How often and when should people self-monitor blood glucose levels? Where (on the body) should people carry out self-monitoring tests?		
Language	English		
Study design	Systematic reviews and RCTs		
Status	Published papers (full papers only)		
Population	Adults (aged 18 years and over) diagnosed with type 2 diabetes. Specific patient sub-groups for whom the management of type 2 diabetes may vary, this may include but is not restricted to: • Older adults • People with renal impairment • People in specific ethnic groups • People in specific cardiovascular risk groups		
Intervention	self-monitoring of blood glucose levels using lancets		
Comparator	No self-monitoring of blood glucose, standard or usual care, self-monitoring of urine glucose, other types of self-monitoring of blood glucose (such as augmentation via education, telecare, continuous glucose monitoring; or different aspects of treatment for example frequency and location of testing)		
Outcomes	Changes in blood glucose levels (HbA1c, fasting and postprandial blood glucose)		

	Details	Additional comments	Status
	Frequency, severity and timing of hypoglycaemic episodes Adverse events The development of microvascular and macrovascular complications: • retinopathy (specific lesions or macular changes, referable retinopathy, blindness/loss of vision, visual acuity) • kidney damage (eGFR, serum creatinine, proteinuria, microalbuminuria, dialysis) • cardiovascular disease (myocardial infarction, heart failure, stroke, ACS, TIA, revascularisation and stenting) • foot complications (amputations, diabetic foot ulcers, charcot osteoarthropathy, diabetic foot infection) Health-related quality of life Resource use and cost		
Other criteria for inclusion/exclusion of studies	**Include:** • Studies focusing on the use of self-monitoring (as part of an overall education package) in people with type 2 diabetes (this will include people who are receiving lifestyle/dietary interventions alone or in combination with blood-glucose lowering therapies) • Studies with a minimum follow-up of 4 weeks **Exclude:** • Non-randomised evidence (including cohort studies, case–control studies and case series), narrative reviews, conference abstracts, letters and editorials • Studies examining a mixed population of people with type 1 and 2 diabetes (unless subgroup analyses are reported or 85% or more of the study population have type 2 diabetes)		At GDG 1, the group agreed that specifying a minimum follow-up over one month may lead to the loss of important information about short-term outcomes such as hypoglycaemia
Search strategies	Systematic reviews and RCTs. Searches can be restricted from 2007-present as CG66 reviewed evidence from 2001-2007.	CG66 included search for qualitative studies (requested by GDG)	
Review strategies	The NICE methodology checklist for RCTs and systematic reviews will be used as a guide to appraise the quality of individual studies Data on all included studies will be extracted into evidence tables Where statistically possible, a meta-analytical approach will be used to		

	Details	Additional comments	Status
	give an overall summary effect All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. Outcomes from previously included studies will be incorporated into the analysis and GRADE profiles where appropriate. Sub-group analysis will be undertaken when appropriate		
Identified key studies	N/A		

C.5.1.6 Review question 6: Should aspirin and/ or clopidogrel be used for primary prevention of cardiovascular disease in people with type 2 diabetes?

	Details	Additional comments	Status
Review question 6	Should aspirin and/or clopidogrel be used for primary prevention of cardiovascular disease in people with type 2 diabetes?	This relates to off-label use but was agreed as a review question due to the use of these drugs in current practice.	
Objectives	• Should aspirin and/or clopidogrel be used to prevent cardiovascular disease in people with type 2 diabetes? • Should all people with type 2 diabetes use aspirin and/or clopidrogel or should this be restricted to specific sub-groups of the population (e.g. does this include people with a lower CV risk?) • When should aspirin and/or clopidogrel be used? • What adverse events and/or safety concerns are associated with the use of aspirin and/or clopidogrel?		
Language	English		
Study design	Systematic reviews and RCTs		
Status	Published papers (full papers only)		
Population	Adults (aged 18 years and over) diagnosed with type 2 diabetes. Specific patient sub-groups for whom the management of type 2 diabetes		

	Details	Additional comments	Status
	may vary, this may include but is not restricted to: • Older adults • People with renal impairment • People in specific ethnic groups • People in specific cardiovascular risk groups		
Intervention	Aspirin and/or clopidogrel (alone or in combination)	Comparisons of interest: Aspirin vs. placebo Clopidogrel vs. placebo Clopidogrel vs. aspirin Clopidogrel + aspirin vs. placebo Clopidogrel + aspirin vs. aspirin monotherapy Clopidogrel + aspirin vs. clopidogrel monotherapy	
Comparator	placebo or each other (including combinations)		
Outcomes	Adverse events The development of microvascular and macrovascular complications • retinopathy (specific lesions or macular changes, referable retinopathy, blindness/loss of vision, visual acuity) • kidney damage (eGFR, serum creatinine, proteinuria, microalbuminuria, diaysis) • cardiovascular disease (myocardial infarction, heart failure, stroke, ACS, TIA, revascularisation and stenting) • foot complications (amputations, diabetic foot ulcers, charcot osteoarthropathy, diabetic foot infection) Mortality		

	Details	Additional comments	Status
	Health-related quality of life Resource use and cost		
Other criteria for inclusion/exclusion of studies	**Include:** • Trials focusing on the use of aspirin and/or clopidogrel in people with type 2 diabetes **Exclude:** • Trials examining the use of aspirin and/or clopidogrel after acute cardiological events, cardiac interventions or cerebrovascular events • Non-randomised evidence (including cohort studies, case–control studies and case series), narrative reviews, conference abstracts, letters and editorials • Trials examining anti-platelet drugs other than aspirin or clopidogrel (e.g. dipyridamole, prasugrel, ticagrelor etc. as used in secondary prevention) • Studies examining a mixed population of people with type 1 and 2 diabetes (unless subgroup analyses are reported or 85% or more of the study population have type 2 diabetes)		At GDG 1 the group agreed that there were clinical reasons why the use of these drugs would differ depending on the type of diabetes. Specifically, people with type 2 diabetes may differ to people with type 1 diabetes in terms of age and risk factors for CVD
Search strategies	Systematic reviews and RCTs. A date restriction of 2007-present can be applied as CG66 reviewed evidence from 2001-2007		
Review strategies	The NICE methodology checklist for RCTs and systematic reviews will be used as a guide to appraise the quality of individual studies Data on all included studies will be extracted into evidence tables Where statistically possible, a meta-analytical approach will be used to give an overall summary effect All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. Outcomes from previously included studies will be incorporated into the analysis and GRADE profiles where appropriate. Sub-group analysis will be undertaken when appropriate		
Identified key studies	N/A		

C.5.1.7 Review question 7: What pharmacological treatment should be used to manage erectile dysfunction in men with type 2 diabetes?

	Details	Additional comments	Status
Review question 7	What pharmacological treatment should be used to manage erectile dysfunction in men with type 2 diabetes?		
Objectives	Should the following pharmacological treatments be used to manage erectile dysfunction in men with diabetes either alone or in combination: • Phosphodiesterase 5 (PDE-5) inhibitors • Testosterone therapy • Alprostredil Should the use of pharmacological treatment for erectile dysfunction be restricted to specific sub-groups of the population? What adverse events and/or safety concerns are associated with the use of testosterone therapy,PDE-5 inhibitors and alprostredil?		
Language	English		
Study design	RCT and systematic reviews		
Status	Published papers (full papers only)		
Population	Men (aged 18 years and over) diagnosed with diabetes (type 1 and 2) Specific patient sub-groups for whom the management of type 2 diabetes may vary, this may include but is not restricted to: • Older adults • People with renal impairment • People in specific ethnic groups • People in specific cardiovascular risk groups		
Intervention	Testosterone therapy, PDE-5 inhibitors and alprostredil (alone or in combination)	Comparisons of interest: Testosterone therapy vs. placebo Testosterone therapy vs. PDE-5 inhibitors Testosterone therapy + PDE-5 vs. either alone PDE-5 vs. PDE-5	

	Details	Additional comments	Status
		PDE-5 vs. placebo Alprostredil (alone or in combination) vs. placebo	
Comparator	Placebo, standard care (or other treatment)		
Outcomes	Erectile function (assessed using validated scale/measure such as International Index of Erectile Function; IIEF) Adverse events The development of microvascular and macrovascular complications Health-related quality of life Resource use and cost		At GDG 1 the group discussed that rates of withdrawal (due to adverse events) would be useful outcomes to be reported. It was agreed that this would fall under adverse events and where reported in trials, this data would be extracted.
Other criteria for inclusion/exclusion of studies	**Include:** • Trials examining the use of testosterone therapy, PDE-5 inhibitors and alprostredil (alone or in combination) for the management of erectile dysfunction in men with diabetes **Exclude:** • Non-randomised evidence (including cohort studies, case–control studies and case series), narrative reviews, conference abstracts, letters and editorials • Diagnosis of erectile dysfunction • Use of testosterone therapy in men who do not have erectile dysfunction		At GDG 1 the group agreed that the overall clinical management of erectile dysfunction may be similar for both type 1 and type 2 diabetes. However it was also agreed that people with type 2 diabetes may differ compared with people with type 1 diabetes in factors such as age and risk factors for CVD
Search strategies	RCT and systematic reviews only Date restriction for PDE-5 inhibitors (2007 onwards)	The full literature search for this review question was extended to cover diabetes (both type 1 and type 2)	
Review strategies	The NICE methodology checklist for RCTs and systematic reviews will be used as a guide to appraise the quality of individual studies		

	Details	Additional comments	Status
	Data on all included studies will be extracted into evidence tables Where statistically possible, a meta-analytical approach will be used to give an overall summary effect All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements. Outcomes from previously included studies will be incorporated into the analysis and GRADE profiles where appropriate. Sub-group analysis will be undertaken when appropriate		
Identified key studies	N/A		