Protocol for MTA of SGLT2 inhibitors (NICE ID 756) 4th March

1. Title: **Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes**

2. TAR team: Warwick Evidence

Lead;

Professor Norman Waugh

Warwick Evidence

Division of Health Sciences

University of Warwick

Coventry CV4 7AL norman.waugh@warwick.ac.uk 02476 151585

Team;

Dr Ewen Cummins, health economist, McMDC, Glasgow

Dr Rhona Johnston, Computer Modeller, McMDC Ltd., Glasgow.

Dr Pamela Royle, information scientist

Dr Christine Clar, researcher in systematic reviews

Dr Saran Shantikumar, academic fellow in public health medicine

Systematic reviewer to be identified

Dr Bee Tan, associate professor Obstetrics and Gynaecology, Warwick Medical School, and consultant in Gynaecology and Obstetics, Birmingham

Dr Paul O'Hare, associate professor, Metabolic and Vascular Health, Warwick Medical School, and diabetologist University Hospitals Coventry and Warwickshire

Dr Tim Holt, senior clinical research fellow, Nuffield Dept of Primary Care Health Sciences, University of Oxford, and general practitioner, Banbury

3. Plain English summary

Type 2 diabetes is a chronic metabolic disorder characterised by raised blood glucose levels (hyperglycaemia). Blood glucose levels are regulated by insulin, a hormone produced by the beta cells in the pancreas. In type 2 diabetes, insulin doesn't work as well as usual because some tissues in the body, such as liver and muscle, are less sensitive to the action of insulin – this is called "insulin resistance". This is followed by a loss of capacity to produce insulin in the pancreas. By the time type 2 diabetes is diagnosed, there has already been a considerable loss of beta cell capacity.

Type 2 diabetes (T2DM) affects more than 3 million people in England. The prevalence of type 2 diabetes has been increasing, partly due to demographic change, partly due to better detection, but mainly due to increased prevalence of overweight and obesity. Diabetes is increasingly costly to the NHS, with a recent study [1] estimating that 10% of all NHS expenditure is on diabetes.

The condition is initially treated by lifestyle advice, aimed at reducing calorie intake and weight, and increasing physical activity. If that fails, then the first choice of drug is metformin tablets. However not everyone can take metformin. This is partly because there are some conditions such as chronic kidney failure which are contra-indications to its use, and partly because around 10% of people get troublesome diarrhoea and have to stop it.

Type 2 diabetes is usually a progressive disease, because the ability of the pancreas to produce insulin falls further over time. When metformin alone is no longer sufficient to keep blood glucose levels normal, other, mainly oral, drugs are added. If these become insufficient insulin is started.

Control of blood glucose levels is important because uncontrolled diabetes can lead to adverse effects, traditionally known as the complications of diabetes. These include damage to the eye (retinopathy) which can cause visual loss, to the kidneys (nephropathy) which can lead to renal failure and a need for dialysis or transplantation, and to the nerves (neuropathy) which can cause unpleasant symptoms and lead to amputation. However the main complication of diabetes is an increased risk of coronary heart disease.

We note that the draft for the NICE Type 2 diabetes guideline update, which is out for consultation, suggests that an Hba1c of 7.5% should be the switching point for intensification (as in CG 87) aiming at a target of 7.0% (Section 1.3.4). In section 1.5, Recommendation 38, the target of 6.5% is suggested for most adults managed on the combination of diet and a single drug not associated with hypoglycaemia. However the draft guideline notes the need for individualised setting of targets.

There are now nine different types of drug for lowering blood glucose in type 2 diabetes (counting all forms of insulin as one type). The newest type of drug acts by causing glucose to be lost in the urine, thereby not only lowering the level in the blood, but also causing a loss of calories which helps to reduce weight. In this document, we refer to them in short as the "flozins". They are taken as tablets.

4. Decision problem

The aim of this technology assessment report (TAR) is to determine the clinical effectiveness, safety, and cost-effectiveness of canagliflozin, dapagliflozin and empagliflozin monotherapy within their respective licensed indications for treating type 2 diabetes.

Interventions

The sodium glucose co-transporter 2 (SGLT2) receptor inhibitors are hereafter referred to as the flozins. Above a certain level, the glucose in the blood passes into the urine through the glomeruli, but is reabsorbed in the renal tubules through the SGLT2 transport system, which is responsible for 90% of glucose reabsorption by the kidney. The SGLT2 inhibitors block this transport system, reducing the reabsorption of renal filtered glucose and promoting excretion of glucose in the urine, helping to control hyperglycaemia.

There are currently three flozins licensed for use in the UK, canagliflozin, dapagliflozin and empagliflozin. The marketing authorisations for use in monotherapy are similar; "in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance". All have been recommended by NICE, but so far, NICE has only considered these drugs in combination therapy.

This TAR will examine their use in monotherapy, in people who cannot take metformin.

NICE guidance

NICE clinical guideline (CG) 87 (a partial update of CG66) 'the management of type 2 diabetes' currently recommends that if lifestyle intervention is insufficient, the first line of drug treatment is metformin. However 10-15% of people with type 2 diabetes cannot take metformin, either because they cannot tolerate it, or because of contraindications to use. The intolerance is usually because of gastrointestinal side-effects such as diarrhoea, especially with higher doses. The main contraindication is chronic renal impairment, and NICE recommends that it should not be used if estimated glomerular filtration rate (eGFR) is below 30ml/minute, and used with caution if eGFR is in the range <45ml/min to >30ml/minute.

In people who cannot take metformin, CG87 currently recommends a sulphonylurea such as gliclazide. A draft update to CG87, currently undergoing consultation, recommends considering repaglinide as the initial drug treatment if metformin is unsuitable, and, if treatment with repaglinide does not control HbA1c, pioglitazone, a sulfonylurea or a dipeptidyl peptidase-4 (DPP-4) inhibitor.

The following is the decision problem for this topic:

Population

People with type 2 diabetes for whom metformin is not tolerated or is contraindicated.

Interventions

- Canagliflozin 100mg and 300mg
- Dapagliflozin 10mg

- Empagliflozin 10mg and 25mg.

Comparators

The scope from NICE lists the following comparators;

- Repaglinide
- Sulfonylureas (gliclazide as representative of the sulphonylureas)
- Pioglitazone
- DPP-4 inhibitors (hereafter referred to as the gliptins)

The three flozins will also be compared with each other.

Outcomes

- mortality
- complications of diabetes, including cardiovascular, renal and eye
- HbA1c/glycaemic control
- body mass index
- frequency and severity of hypoglycaemia
- changes in cardiovascular risk factors, including total cholesterol, HDL cholesterol and systolic blood pressure
- adverse effects of treatment, including urinary tract infections, genital infections and malignancies
- health-related quality of life.

Outcomes will be reported at six months and where data permits at 12 months or longer.

We will grade hypoglycaemia as severe, moderate and minor and attribute disutilities to the first two. We will take into account that hypoglycaemia is often under-reported unless specifically enquired about. Observational studies may be a better guide to frequency than RCTs.

5. Report methods – clinical effectiveness

Search strategy: standard methods, using Medline, Embase and all sections of the Cochrane Library. Websites of pharmaceutical companies and trial registries will be checked for research in progress. Conference abstracts from ADA 2015 (June) will also be checked.

Types of study:

- Randomised controlled trials (RCTs) for efficacy
- Observational studies for safety data, and effectiveness and acceptability in routine care
- Evidence review group (ERG) reports from previous appraisals of the three drugs for safety aspects.

- For all types of study, minimum durations of 24 weeks or more will be used, with preference given to longer duration trials. Shorter duration trials will be excluded.
- Network meta-analyses of the flozins and other drugs in monotherapy will also be sought.

Subgroups: if data permit;

- Body mass index (BMI) <25, 25-29, 30 and over
- baseline HbA1c
- for adverse effects, men and women separately

Study selection criteria

Lists of studies found in the searches will be checked by two people independently.

Conference abstracts will be treated with caution due to the inevitable lack of detail. They may be used as a guide to emerging research. Data in abstracts may be used if full details of studies have previously been published as protocols, or if the abstract reports extensions of previously reported trials.

Quality assessment

- RCTs – Cochrane risk of bias method
- NMAs – Donegan et al (2010) checklist.
- Observational studies – Newcastle-Ottawa checklist

Notes:

The patients involved will be those who cannot take metformin. One issue will be that trials of other drugs as monotherapy will not be only in patients that have not been able to tolerate metformin. It may be necessary to assume that the effectiveness of other drugs is no different in those who get gastro-intestinal adverse effects with metformin, than from those who can tolerate it. However some renal function restrictions also apply to other drugs such as the flozins.

A search will be carried out for studies that compare people who can and cannot tolerate metformin, looking for any differences in factors that might affect the modelling, such as weight, blood pressure, and cholesterol.

As noted above, type 2 diabetes is usually a progressive disease. However some patients may achieve good results with the combination of diet, physical activity and monotherapy, and may remain on that combination. Searches will be carried out to determine what proportion do so, and what their characteristics are.

6. Network meta-analysis

We expect to find few head to head trials in monotherapy, and an NMA will be necessary to make inferences on the comparative effectiveness. Trials will be included if sufficiently similar in terms of duration, baseline characteristics, absence of prior drug therapy, comorbidities, and quality of study. We expect the common comparator to be placebo. Consideration could be given to using metformin as a common comparator, but this would require an assumption that effects on the parameters that would be most important in the NMA – HbA1c, weight, blood pressure, cholesterol – would be similar in patients who can and cannot tolerate metformin.

In order to assess statistical coherence, indirect results from the NMA will be compared with direct results, where available. Heterogeneity of trials of same drug and comparator will be assessed by inspection and tested by Cochran's Q and quantified by using I^2. Conceptual heterogeneity will be assured at inclusion stage. Despite this, a random effect model will be used for safety. Drugs will not be ranked, but will be considered in terms of effect sizes and uncertainties. Credible intervals will be used.

In theory, comparison of the individual flozins might show that one is superior, in which case that would be the flozin used in further analyses such as comparison with non-flozin comparators. However it is not expected that any head to head trials of flozins compared with each other will be found, and so any comparison would be based on the NMA. If differences in effectiveness are seen amongst the three flozins, we do not expect these to be large, and the uncertainties inherent in NMAs would probably make it unsafe to conclude that any one flozin was best.

7. Cost effectiveness

For cost and utility estimates, we will in the first instance rely upon the publications from the UK Prospective Diabetes Study (UKPDS). Cost and utility data from the updated NICE clinical guideline on type 2 diabetes will also be used.

A wider review of the literature will only be undertaken if these do not provide all the cost and utility data required.
If any cost-effectiveness studies are included, they will be quality assessed using the using the Drummond (1996) checklist.

We plan to use the updated UKPDS/Oxford model (OM2) which is due to be released at end of March. It is an update of the original UKPDS/Oxford model (OM1). The model uses patient data taken from the UKPDS and simulates total burden of disease over an extrapolated lifetime for a population with type 2 diabetes, to measure the effects of treatments. However, the OM2 requires a wider set of inputs than OM1 (see below). Therefore OM1 will be used if not all available information is available for OM2 (with OM2 assumptions possibly being used in a scenario analysis), or if the final implementation of the OM2 proves impossible to design an appropriate "front end" for as had to be undertaken for the OM1 during the modelling that underlies the draft NICE clinical guidelines:

- OM1 requires estimates of the effects of treatments upon HbA1c, blood pressure, and the HDL- cholesterol to total cholesterol ratio with the impacts upon BMI, hypoglycaemia events and adverse events also being required to be added to this.
- OM2, in addition to the variables of OM1, requires estimates of the impact of treatments upon HDL, LDL and total cholesterol levels, patient heart rate, estimated glomerular filtration rate, the presence of micro or macro albuminuria, the white blood cell count and the haemoglobin concentration.

Note that as outlined above, these clinical effectiveness estimates are required not only for the initial monotherapies, but also for the subsequent intensifications of therapy.

The cost-effectiveness approach will be:

- Obtain from the clinical effectiveness section the inputs will be necessary for OM1 and a wider set of variables for using OM2 (depending on what the final form of OM2 will require)
- Clinical effectiveness data will include HbA1c, SBP, and TC:HDL ratio as drawn from the clinical review section and the NMA, supplemented by additional review of the clinical effectiveness for the subsequent intensifications of therapy.
- Depending upon the results of the clinical section and data available, options include:
    - Use OM1 as not all variables for OM2 available from clinical review this or OM2 proves impossible to design an appropriate front end for; or,

    - Use OM2 as sufficient variables available from clinical review for this; or,
    - Use OM1 for the base case as not all variable for OM2 available from clinical review, but explore the impact of using OM2 with some additional assumptions about the unavailable variables; or,
- In the first instance we will rely upon the UKPDS publications for costs and QoL estimates possibly augmented by the recent CG, and only go outside of these if they seem insufficient.

Scenarios of treatment changes will also be modelled with each treatment change being modelled once a patient's HBA1c rises above 7.5%. The clinical effectiveness of each of these subsequent lines of therapy will be assumed to be the same across the comparator arms that are modelled, unless the evidence suggests otherwise.

The treatment sequences will take account of licensed indications – drugs licensed for use in dual therapy only in combination with metformin will be excluded. Sequences will take note of the recommendations in the draft clinical guideline for type 2 diabetes. If intensification requires insulin, NPH insulin will be used. The flozins, and the gliptins and pioglitazone, are approved for monotherapy only among those for whom metformin is contraindicated. The intensifications of therapy subsequent to monotherapy and the resulting treatment pathways will be informed by those outlined in the current draft NICE clinical guideline for patients contraindicated to or intolerant of metformin. For the base case this suggests that intensifications of therapy occur when HbA1c reaches 58mmol/mol (7.5%), and that the following treatment sequences should be considered:

- Repaglinide -> pioglitazone + sulfonylurea
- Pioglitazone -> pioglitazone + sulfonylurea
- Sulfonylurea -> gliptin + sulfonylurea
- Gliptin -> gliptin + sulfonylurea

The draft guideline suggests choosing the gliptin with the lowest acquisition cost.

Monotherapy with the flozins is not covered by the current draft guideline. For consistency, the base case will assume the same intensification pattern as for pioglitazone and the gliptins:

- Flozin -> flozin + sulfonylurea -> NPH

For the first intensification, most monotherapies are assumed to have a sulfonylurea added to them. The clinical effects of intensification through the addition of a sulfonylurea will be assumed to be the same across the arms, unless there is evidence that suggests otherwise. Clinical effectiveness estimates will also be required for the intensification of therapy from monotherapy repaglinide to pioglitazone plus sulfonylurea, and for the intensification of therapy from monotherapy sulfonylurea to a gliptin plus sulfonylurea.

For the second intensification, clinical effectiveness estimates will be required for the move to NPH. These clinical effectiveness estimates will be assumed to be the same across the arms, unless there is evidence that suggests otherwise. A scenario analysis of patients intensifying to glargine may also be undertaken.

The modelling approach will be guided to a large extent by the current draft NICE clinical guideline, and in particular the full economic report of appendix F of the draft guideline. As in appendix F of the draft guideline, for cost and utility estimates we will in the first instance rely upon the usual UKPDS publications and the new clinical guideline on type 2 diabetes, and only if these appear incomplete or insufficient will we undertake a wider review of the literature.

If we review any cost-effectiveness studies, we will quality assess them using Drummond (1996) checklist.

8. Company submissions

Any unpublished RCTs provided will be assessed and summarised.

We will consider the findings of the company's cost-effectiveness analyses, with particular attention to the ICERs therein. If the company's ICERs differ from those generated by our analysis, the clinical data and assumptions used to derive them will be explored to determine why their conclusions differ. Detailed critiques of company models will not be undertaken.
The economic approaches from companies will be assessed using the NICE reference case checklist.

9. Timelines

Final protocol to NICE 3rd March

Draft report to NICE 24th August

Final report to NICE 23rd September

Company comments on report due 5th November, and our responses to NICE by 12th November.

First Appraisal Committee meeting 25th November

References

1. Lex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of Type 1 and type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabetic Medicine 2012/29/855-862*

Drummond, M. *Guidelines for authors and peer reviewers of economic submissions to the BMJ.* BMJ 1996;313:275