Individualising care for patients with type 2 diabetes is a central theme in both the American Diabetes Association/European Association for the Study of Diabetes and NICE treatment guidelines. This individualisation involves setting an appropriate target HbA1c for an individual patient and determining choice of treatment primarily by risk of specific side effects and cost. Treatment could also be individualised by identifying subgroups of patients who respond particularly well to one type of glucose-lowering therapy and/or have altered risk of treatment-specific side effects. As this applies to groups or strata of patients rather than an individual it has been termed ‘stratification’. A clear example of stratification in diabetes is that patients with HNF1A MODY have a 4-fold better response to sulphonylureas than matched subjects with type 2 diabetes. This means excellent glycaemic control can be achieved in these patients using very low sulphonylurea doses.

Type 2 diabetes lacks the homogeneity of a single gene disease: can we therefore identify subgroups of patients within this group who will respond better to one type of glucose-lowering therapy? On the face of it this should be possible; glucose-lowering therapies act at different sites and have different mechanisms of action, and patients have differing pathophysiology even when they have a similar degree of hyperglycaemia. Although theoretically attractive, to date the evidence for specific subgroups having a differential response has been limited. This mainly reflects very little work being done to identify subgroups who respond well or badly to a medication and even less trying to identify subgroups where a specific treatment is favoured over another.

Guidelines for treatment in the absence of data on stratification of glucose lowering

In the absence of information about which patients will have the best glycaemic response to a therapy and limited data on comparative effects on long-term outcomes it is hard to give guidance. This results in the present algorithm for second and third line therapy seen in the recent NICE guidance where the drugs are listed in alphabetical order with limited guidance given on how to choose the optimum therapy. Data on prescribing in the UK show primary care doctors usually favour metformin and sulphonylurea as first and second line therapy. Third line treatment used to be insulin but now there is a wide choice of three oral therapies – thiazolidinediones, DPP-4 inhibitors (gliptins) and SGLT2 inhibitors as well as injectable GLP-1 receptor agonists and insulin. Guidance on which therapies are likely to be most effective for an individual would be helpful to ensure patients receive a treatment most likely to be effective for them, and minimise cost, side effects and hyperglycaemia associated with initiation of an ineffective treatment.

Current third line treatment

Abbreviated NICE guidelines for third line therapy are shown in Figure 1.

Preliminary data proposing possible stratification of glycaemic response in type 2 diabetes

MASTERMIND is a Medical Research Council funded collaboration examining stratification in type 2 diabetes involving academic centres (Universities of Exeter, Dundee, Oxford, Glasgow, Bath, Newcastle, and King’s College London) and the pharmaceutical industry. It aims to confirm variation in subgroup response to therapy and assess how this response is related to clinical features. Identification of these subgroups and evidence of improved or reduced response to a range of drug mechanisms will provide guidance in choice of glucose-lowering therapy.

Early work of this consortium and others has shown that such stratification is possible and that response to a therapy may be based on clinical characteristics and biological mechanisms. The PRIBA study of patients starting GLP-1 receptor agonist therapy showed patients with low beta-cell function, characterised by low C-peptide and positive GAD or IA2 islet antibodies, had a markedly reduced response.

The group have also used routine GP data from over 110 000 patients with type 2 diabetes together with data

Crossover studies can help the individualisation of care in type 2 diabetes: the MASTERMIND approach

Catherine Angwin, Ewan Pearson and Andrew Hattersley

Second intensification. HbA1c rises to 58mmol/mol (7.5%)

Option 1. Triple therapy with:
- Metformin, a sulphonylurea and a DPP-4 inhibitor
- Metformin, a sulphonylurea and pioglitazone
- Metformin, a sulphonylurea or pioglitazone

Option 2. Insulin-based treatment

Aim. HbA1c level of 53mmol/mol (7.0%)

Figure 1. Abbreviated NICE guidelines for third line therapy
from clinical trials to identify potential stratification. These include obese patients who experience a better glycaemic response when compared to non-obese patients when taking thiazolidinediones, but do worse when taking glitins. Also, within the normal range a higher GFR is associated with a better response to SGLT2 inhibitors, which inhibit the active reabsorption of glucose in the proximal tubule, while patients with a reduced but still normal GFR may see better glycaemic response when taking a renally-excreted glitin.

These are simple, mechanistically intuitive observations which would easily transfer to clinical practice; BMI and GFR do not require expensive diagnostic tests. Having established differential response and identified associations between this response and drug mechanism, this potential stratification now needs to be tested in a trial.

**New approaches to test potential stratification**

The lack of previous work on differential response between subgroups leaves little methodological groundwork on which to build. The pilot work by the academic investigators and discussions with industrial colleagues quickly identified the need for new approaches to trials if new stratified approaches to therapy were to be found. The challenge has been to identify an approach which combines the identification of subgroups that will respond well to one therapy and less well to another therapy. Randomised control trials (RCTs) with parallel-arm comparison do not try more than one therapy in the same patient.

In analgesia therapy, n-of-1 trials have been used successfully to find the best drug for an individual patient by allowing them to try multiple therapies and choosing the best option for them. They are clearly superior in choosing the best treatment for an individual but lack the generalisability and robust evidence of an RCT.

Crossover trials have the clear advantage of patients acting as their own control which reduces between-patient variability; the comparison of treatments is made on the same patient. This reduces the sample size needed compared to a parallel group trial design as well as cost. Randomised crossover trials can also be used to test specific subgroup hypotheses. Type 2 diabetes lends itself to crossover trials as a stable chronic condition with an easily measurable outcome in glycated haemoglobin (HbA1c). The existence of multiple third line therapies with little guidance makes a crossover trial an ideal approach to stratification in this group of patients.

**TriMaster trial – a new study to test stratification**

TriMaster is the first three-way crossover study of third line glucose-lowering oral therapies, using an on-treatment HbA1c result as a primary outcome.

It will test whether an informed evidence-based decision could be made on an individual’s likely response to therapy. In all, 600 patients on metformin and a sulphonylurea, with an HbA1c >58mmol/mol, will be recruited at 20 centres nationwide from the summer of 2016 for three years. These patients, who meet NICE guidelines for addition of a third line treatment, will have underlying pathophysiology assessed in a mixed-meal tolerance test (MMTT) and baseline samples collected for analysis and storage for future biomarker discovery. (Figure 2.) They will receive 16 weeks of the three available oral therapies blinded, and in random order. At the end of each 16-week treatment arm an on-treatment HbA1c will be taken and the three values compared at the study conclusion. Crucially, the measure analysed will be the achieved value after 16 weeks rather than percentage or absolute change between either study or therapy baseline and end of treatment arm.

TriMaster will test two specific hypotheses that are based on preliminary trial and routine data. Firstly, that obese patients with a raised BMI (>30kg/m²), compared to non-obese patients, will respond well to pioglitazone and less well to sitagliptin. Secondly, that patients with modestly reduced eGFR (60-90ml/min/1.73m²) compared to those with eGFR >90 will respond well to sitagliptin and less well to canagliflozin. Patients will be randomised to four strata based on BMI and eGFR to ensure evenly-sized groups, and the inclusion criteria will include all those who would be eligible for the three drugs in clinical practice.

The crossover design has been carefully considered to avoid any discontinuation of third line therapy as washouts in the much shorter pilot study saw steadily increasing HbA1c and withdrawal from the study. A carry-over effect has been minimised by a 16-week treatment period, where the final HbA1c reflects glycaemia over the preceding eight to 12-week period and all three drugs have no continuing glucose-lowering effect one to four weeks after discontinuation. Residual carry-over and

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**Figure 2. TriMaster study diagram**

<table>
<thead>
<tr>
<th>Patient on metformin and sulphonylureas with HbA1c &gt;58mmol/mol</th>
<th>Baseline HbA1c and mixed-meal tolerance test</th>
<th>4 months DPP-4 inhibitor or SGLT2 inhibitor or thiazolidinedione</th>
<th>4 months DPP-4 inhibitor or SGLT2 inhibitor or thiazolidinedione</th>
<th>4 months DPP-4 inhibitor or SGLT2 inhibitor or thiazolidinedione</th>
<th>HbA1c</th>
<th>HbA1c</th>
<th>HbA1c</th>
<th>Patient preference</th>
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<td>DPP-4 inhibitor or SGLT2 inhibitor or thiazolidinedione</td>
<td>DPP-4 inhibitor or SGLT2 inhibitor or thiazolidinedione</td>
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<td>DPP-4 inhibitor or SGLT2 inhibitor or thiazolidinedione</td>
<td>HbA1c</td>
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<td>HbA1c</td>
<td>HbA1c</td>
</tr>
</tbody>
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**Leader**
treatment period interaction or order effect will be assessed at analysis.

Side effects and patient preference
Prescription of additional treatment in type 2 diabetes is already individualised by risk of side effects, whether evidence based or anecdotal. These risks are supported by trial and clinical data, but are based upon an average risk only. A prescribing clinician cannot balance risk against potential benefit in an individual patient because they lack evidence of subgroup response and individual risk of side effects. To improve individualised care they need to link a patient’s likely response to their risk of side effects.

A further advantage of the crossover approach is that a secondary outcome of patient preference and side effects can be assessed. TriMaster will collect data on patient experience of side effects and overall preference. Differential subgroup response to the three therapies will then be compared to incidence of side effects. These data and continuing exploration of routine clinical and trial data will establish any association of side effects and response, and ask if it is possible to assess within a given subgroup of response whether some patients are more likely to experience side effects.

Side effect data will include not only incidence and severity, but acceptability: the patient’s tolerance and willingness to take the therapy long term. The benefit of allowing patients to compare therapies will provide an insight into their decision process in clinical practice. Would an obese patient be prepared to tolerate a small percentage weight increase if accompanied by a pronounced improvement in HbA1c, or would a patient already prone to thrush be unwilling to increase this risk and opt for a drug which may be less effective in lowering glucose? In the end it is the patient who should make this choice, and this type of study will let them compare their experiences on three different drugs.

Stratification long term
Robust evidence for stratification by subgroup response, favoured therapy or experience of side effects would be a leap forward in therapy choice in type 2 diabetes. A long-term objective is for international and national patient care pathways to include, for the first time, evidence on which therapy is the most appropriate for specifically-defined subgroups of patients based on glycaemic response and side effect profile. We hope the TriMaster study will be a first step in this direction.

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Declaration of interests
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