# Type 2 Diabetes Prevention in High-risk Individuals: how might Effective, Equitable and Sustainable Service Provision be Achieved?

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DECLARATION

I declare that this doctoral statement is my own work and I have correctly acknowledged any work of others, in accordance with University and Institute guidance on good academic conduct, and that no part of the material offered has been previously submitted for a degree or other qualification in this or any other university. Where joint work is submitted my independent contribution is outlined within the appropriate co-authorship forms.

Signature: 

Date: 22.05.2014

## ABSTRACT

**Background:** Prevalence of type 2 diabetes (T2D) is rapidly increasing worldwide, linked to the obesity epidemic. There is substantial research evidence for T2D prevention by lifestyle interventions in high-risk individuals. The span of this research provides a unique case study with which to critically examine general guidance for development and evaluation of interventions to improve health.

My research question is how might can effective, equitable and sustainable service provision for T2D prevention in high-risk individuals be achieved?

**Methods:** Five papers reporting my empirical T2D prevention research form the core of my thesis. This research extends from the European Diabetes Prevention Study (EDIPS) RCT to the 'New life, New you' (NLNY) feasibility study. NLNY is a community based lifestyle intervention to reduce T2D incidence that is delivered by fitness trainers in North East England.

To inform my research question I have reviewed intervention guidance history. I have then used T2D prevention as a case study, supported by my empirical research experience, to analyse this guidance

**Findings:** Development of the NLNY intervention built on the EDIPS RCT evidence and experience. Pilot evaluation of NLNY suggests a feasible and acceptable intervention that is likely to be effective in preventing T2D. Prevention of T2D provided a useful exemplar for analysis of intervention guidance and highlighted strengths and limitations of existing guidance models. This analysis led to a proposed new guidance framework.

**Conclusions:** The NLNY intervention provides a potential service provision model for T2D prevention in high-risk individuals. Well planned effectiveness and cost-effectiveness evaluation of the NLNY intervention is now needed. The analysis of intervention guidance and the proposed new framework will contribute to developing a robust study design. If effectiveness of the NLNY intervention is demonstrated there is potential for this community based intervention model to be further developed and adapted.

## ACKNOWLEDGEMENTS

I wish to acknowledge the contribution to my empirical work made by all the participants in the Newcastle arm of the European Diabetes Prevention Study and all the participants in the 'New life, New you' intervention. I also wish to acknowledge the contribution made to this empirical work by all the many staff who contributed to those studies including the study applicants and steering group members, intervention funders and commissioners, intervention delivery staff in Newcastle and in Middlesbrough and the support staff at Newcastle University. In addition I wish to thank my many co-authors for their contributions to the publications that contribute to my thesis. The collation of the European Diabetes Prevention Study data set would not have been possible without the collaboration of partners in Finland and The Netherlands and I particularly wish to acknowledge the contribution of Jaana Lindström and Annemieke Th. Den Boer to this task. I wish to thank the internal assessors of my thesis, Ruth Bell, Louise Robinson and Vera Araujo-Soares for their clear and helpful advice. I wish to thank my supervisors Martin White and Katie Haighton for their kind, patient and professional guidance. Finally I wish to thank my family for their love and support, especially my two sons and my darling husband.

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**SP3. Translating research evidence to service provision for prevention of type 2 diabetes: development and early outcomes of the 'New life, New you' intervention.** Penn L, Lordon J, Lowry R, Mathers J, Smith W, Walker M, White M. *Br J Diabetes Vasc. Dis.* 2011;11:175-181 (Appendix C)

**SP4. Feasibility, acceptability, and outcomes at 12 months follow-up of a novel community based intervention to prevent type 2 diabetes in adults at high risk: mixed methods pilot study.** Penn L, Ryan V, White M. *BMJ Open; 2013 3(11)* (Appendix D)

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## PREFACE

I studied physiology and biochemistry for my first degree. During the course of study I became fascinated by the complexity of endocrinology, although at that time I thought insulin hormone was the 'easy' hormone. Also I was interested in the inter-relation of biochemical pathways, particularly links between glucose and fat metabolism in healthy physiology. However, after graduation I decided that laboratory science was not the right course for me at that time and I spent some years as a secondary school science teacher. My first post was as a physics teacher and I subsequently decided to keep with this subject area because I enjoyed the challenge involved in communicating complex concepts to young people in ways that facilitated their understanding. Thus, it was not until sometime later, when I joined Newcastle University as a public health researcher, that I revisited my original interest in healthy physiology and the biological determinants of disease.

The public health and health promotion perspective on disease aetiology and preventive interventions is clearly different from the laboratory science and theoretical endocrinology approach to essentially the same subject area. However, a basic knowledge of the fundamental sciences that underpin the rationale for prevention of type 2 diabetes by lifestyle intervention adds a depth to my interest that contributes to a continuing fascination with the topic.

I know that career pathways into public health are various and I believe that this variety of experience enriches discussions. I am pleased to have spent time as a practitioner, even though in the field of education rather than health, and I retain an empathy with real world practitioner perspectives. However, I have finally found the job I love to do and I am so grateful for the opportunity to study for my Doctorate.

# CHAPTER ONE: INTRODUCTION

Prevention of type 2 diabetes (T2D) falls within the sphere of health promotion, which is defined by the Ottawa Charter as 'The process of enabling people to exert control over the determinants of health and thereby improve their health.'[1] The large and rapidly increasing prevalence of T2D worldwide, the debilitating disease complications that affect people's quality of life and incur high treatment costs, together with the potential for preventive intervention, make this a hugely important area of applied research. [2] Although there is a genetic predisposition associated with T2D,[3, 4] it is essentially a lifestyle disease that is strongly linked to obesity and inactivity.[5] Type 2 diabetes (for description see chapter 3) can be prevented or delayed by lifestyle interventions.[6]

My research question is how effective, equitable, and sustainable service provision for T2D prevention might be achieved.

The concept of an evidence base as a desirable contribution, alongside other considerations, to health care practice is now well established.[7] The use of evidence to support public health intervention provision for health improvement and disease prevention has a different focus and is less well defined. The challenges associated with disease prevention include the complexity of lifestyle interventions.[8] Within public health, prevention of T2D is unusual as there is a substantial evidence base for T2D prevention. Evaluations of T2D preventive interventions for high-risk individuals include early feasibility studies, large randomised controlled trials (RCTs), 'real world' translational studies, and service provision models in some countries.[9 10] The span of this research makes T2D prevention a uniquely suitable case study with which to analyse the utility of general guidance for the development and evaluation of complex interventions to improve health.

My empirical T2D prevention research is reported in my five submitted papers that are listed above, introduced with contextual detail in Chapter six, and included in Appendices A to E. These T2D prevention studies have been undertaken over several years. The Newcastle arm of the European Diabetes Prevention Study (EDIPS-

Newcastle) was a clinical trial of lifestyle intervention for T2D prevention.[11] The study protocol was based on the Finnish Diabetes Prevention Study (DPS).[12] The DPS, together with EDIPS-Newcastle and the similar SLIM study from The Netherlands, formed the European Diabetes Prevention Study (EDIPS) collaboration. Following the completion of EDIPS-Newcastle we collated the EDIPS data. The first analysis of the EDIPS data forms the basis of my second submitted paper.[13] The reduction in T2D incidence was similar in each of the contributory studies with a combined reduction of 57% in the intervention groups compared with the control groups. Analysis of the weight loss intermediate health outcome data from EDIPS showed that those who achieved the target weight loss of at least 5% at one year had 65% lower T2D incidence. Maintaining weight loss for two or three years further reduced T2D incidence. The weight loss analysis of the EDIPS data was designed to support the evaluation of the 'New life, New you' (NLNY) pragmatic T2D preventive intervention feasibility study.[14]

My remaining submitted papers report on the feasibility and acceptability of the NLNY intervention that was delivered by health and fitness trainers in leisure and community settings in Middlesbrough, UK.[15, 16] The NLNY intervention lifestyle targets were modelled on the EDIPS study although the risk assessment, inclusion criteria, mode of delivery and study design were all different. The weight loss achieved at one year in the NLNY feasibility study was comparable to that achieved at one year in the EDIPS RCT. This encouraging primary outcome along with successful recruitment to the programme has led to the commissioning of the NLNY intervention as a service provision in Middlesbrough. However, the NLNY intervention effectiveness cannot be demonstrated without an experimental trial.

In association with the NLNY feasibility study I conducted a qualitative study of participants' perspectives of their behaviour change to support the further development of T2D preventive interventions.[17, 18] The NLNY qualitative study is submitted in Appendix E as part of my thesis.

The accumulated evidence and experience from the EDIPS and NLNY intervention studies and their associated qualitative studies underpin future research outlined in chapter eight. This includes a proposed cluster randomised controlled trial of the NLNY intervention.

In 2000 the Medical Research Council (MRC) proposed guidance for development and evaluation of complex interventions to improve health [19] This guidance was updated in 2008.[20] The MRC 2008 guidance framework was developed by a writing group with expert contributions. This framework has become influential both within and beyond the UK, is widely cited and might be considered a standard text. The MRC 2008 framework sits within a historical timeline of similar guidance relating to the development and evaluation of complex interventions to improve health.

To inform my research question I aim to:

1. Review guidance for the development and evaluation of complex interventions to improve health and elicit important aspects of guidance frameworks.

2. Introduce T2D, its aetiology and opportunities for preventive intervention.

3. Review the literature to identify and select T2D prevention studies that illustrate different stages across the intervention development and evaluation spectrum from early feasibility studies to service provision.

4. Analyse the selected T2D prevention studies with reference to the important intervention development and evaluation activities identified from my review of guidance frameworks.

5. Present and reflect on my own T2D prevention work at Newcastle that has progressed in parallel with similar work elsewhere and that has underpinned and informed this guidance analysis.

6. Use information from the preceding four aims (above) to outline the need for revised intervention guidance and propose a new framework diagram.

In the final chapter I will discuss my empirical T2D prevention work and guidance analysis with the implications for policy, practice and future research.

# CHAPTER TWO: REVIEW OF GUIDANCE FOR DEVELOPMENT AND EVALUATION OF COMPLEX INTERVENTIONS TO IMPROVE HEALTH

## 2.1 The historical context of guidance development

To review guidance for development and evaluation of complex interventions to improve health, I have first identified guidance models and positioned these in a historical timeline. The terminology used to describe complex interventions to improve health has changed somewhat over time. For example the term 'health promotion' used in earlier work has been replaced by 'health improvement' or included in 'public health' in later research.[21] In addition, some of the models included in this timeline focus on specific, aspects of intervention development and evaluation; for example a focus on 'evaluability '[22] or 'implementation fidelity.'[23] However, these models have all contributed to the historical picture of guidance development.

Two main approaches to early guidance development are evident from the historical picture. One such approach reflects the biomedical research continuum and was derived from pharmacological research and phased drug trials. The other main approach reflects a sociological perspective and was derived from sociology research roots. The chronological order of guidance relating to the development and evaluation of complex interventions to improve health is outlined in Figure 1 below.

## 2.2 The biomedical research continuum

The biomedical research continuum was summarised graphically as 'Levy's arrow' in the 1982 publication of the director's report to the US National Heart, Lung and Blood Institute (NHLBI) Advisory Council (Figure 2).[24] This report was about allocation of research funding. Levy's arrow outlines three progressive stages from basic research, via applied research and clinical trials, to provision of health services. The identification of a 'Demonstration and Education Programmes' stage between research and practice implementation is a strength of Levy's arrow that has relevance for my research question.

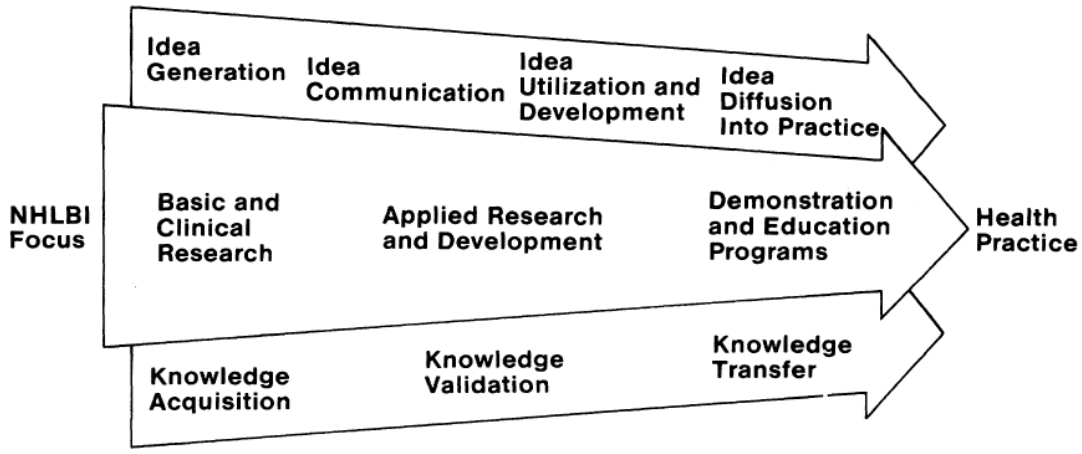
**Figure 1: Historical timeline of guidance relating to the development and evaluation of complex interventions to improve health**

| | | | |
|---|---|---|---|
| 1982 | US | Levy's Arrow, 1982 | The biomedical research continuum (US National Heart, Lung and Blood Institute) |
| | | Flay, 1982 | Phases of research in the development of health promotion programmes |
| 1984 | US | Greenwald & Cullen, 1984 | Phases of cancer control research |
| 1998 | US | Nutbeam, 1998 | Evaluating health promotion |
| 1999 | US | Re-AIM, 1999 | Evaluating the public health impact of health promotion interventions |
| 2000 | UK | MRC 2000/ Campbell M 2000 | Framework for design and evaluation of complex interventions to improve health |
| 2004 | UK | Collins, 2004 | Conceptual framework for adaptive preventive interventions |
| | UK | Greenhalgh, 2004 | A model of diffusion in service organisations |
| 2004 | UK | Pawson & Tilley, 2004 | Realist evaluation |
| 2006 | UK | Cooksey, 2006 | Pathway for translation of health research into healthcare improvement |
| 2007 | UK | May, 2007 | Understanding the implementation of complex interventions in health care: the normalization process model |
| | | Campbell NC, 2007 | Designing and evaluating complex interventions to improve health care |
| 2007 | US | Mercer, 2007 | Study designs for effectiveness and translation research: identifying trade-offs |
| | | Westfall, 2007 | Practice-based research – 'Blue Highways' on the NIH roadmap |
| 2008 | UK | MRC, 2008 | Developing and evaluating complex interventions: new guidance |
| 2008 | US | Feldstein & Glasgow, 2008 | A practical, robust implementation and sustainability model (PRISM) for integrating research findings into practice |
| 2009 | UK | Ogilvie, 2009 | A translational framework for public health research |
| 2010 | US | Breitenstein, 2010 | Implementation fidelity in community based interventions |
| | US | Leviton, 2010 | Evaluability assessment to improve public health policies, programs and practices |
| 2011 | UK | Ogilvie, 2011 | Assessing the evaluability of complex public health interventions: five questions for researchers, funders and policymakers |

**Key to Figure 1**

| | | | | | |
|---|---|---|---|---|---|
| | *Guidance derived from the bio-medical research perspective* | | *Guidance derived from a sociological research perspective* | | *Guidance with a specific focus* |

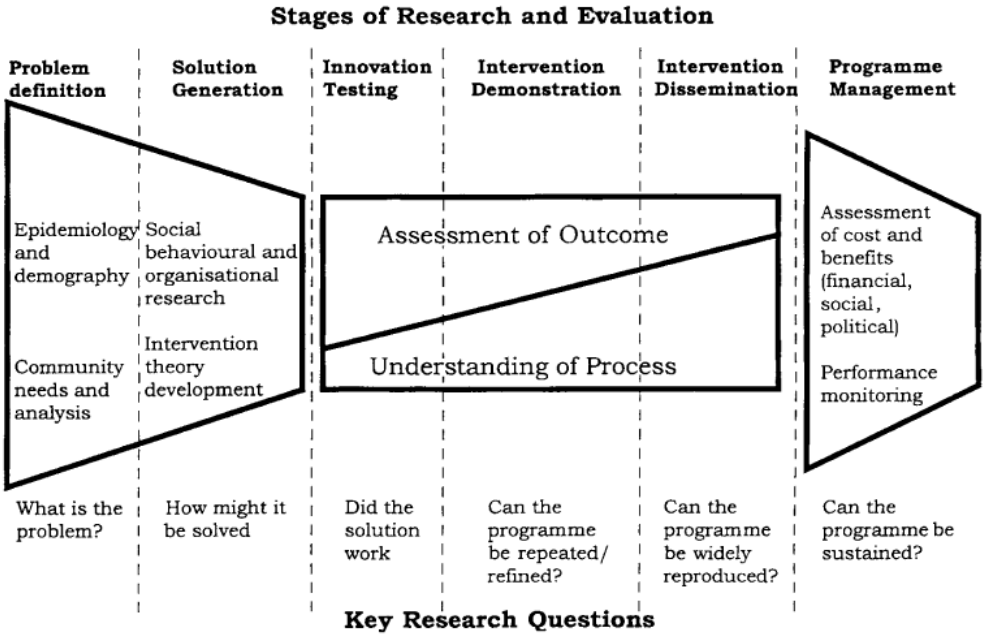
**Figure 2: Biomedical research continuum. US National Heart, Lung, and Blood institute (Levy 1982)**




A similar sequentially staged approach, to the development and evaluation of health promotion interventions, was described in influential papers by Greenwald and Cullen,[25] Flay,[26] and Nutbeam [21] in the 1980-90s. There are five stages identified by Greenwald and Cullen, five identified by Flay and six in the Nutbeam model. The Flay model distinguishes between efficacy trials, treatment effectiveness trials and implementation effectiveness trials. This concept of stage related summative evaluations is a strength of the Flay model and a recurrent theme in my thesis. The distinction between efficacy, described by Flay as a trial to test whether a treatment does more good than harm under 'optimum conditions' (pages 2 and 3) and effectiveness, described by Flay as 'testing whether a treatment does more good than harm when delivered via a real-world program (page 2)' is a useful concept for answering my research question. Flay goes on to distinguish between a health research approach to effectiveness evaluation (where efficacy has been determined) and a program evaluations field approach (where programmes are already operational irrespective of proof of efficacy). Flay stresses the importance of implementation and the need for 'sequencing of studies' (from efficacy via effectiveness to implementation evaluation). He explains the desirability of causal inference that can only be derived from experimental study designs and is also an early advocate of process evaluation. The Flay paper has well-defined concepts and a helpful glossary. Arguably Flay's model lacks detail about developing an intervention to the point where efficacy evaluation is appropriate.

The Nutbeam model starts with 'problem definition' and progresses to 'programme management' with associated key research questions. The gradation from greater importance in assessment of outcome to greater emphasis on understanding of process through the stages, as shown in Figure 3, is a strength of the Nutbeam model and an important theme for sustainable intervention design. Nutbeam also describes public health outcomes and their value as judged from different perspectives and organisational levels (individual, community, society), which is a further strength. Nutbeam refers to 'The evolution of the concept of health promotion' (page 1) and highlights the importance of structure and sequence in establishing the credibility of health promotion.[21] Arguably Nutbeam's model lacks detail within each stage, but it is easy to assimilate and has proved influential.

**Figure 3: Six-stage development model for the evaluation programmes (Nutbeam 1998)**




In the MRC 2000 framework, complex interventions were described as comprising, 'a number of separate elements which seem essential to the proper functioning of the intervention' (page 1).[19] None of the preceding models (described above) are referenced in the MRC report or the associated British Medical Journal (BMJ) paper [27]although the staged progression paradigm is similar. The MRC 2000 framework distinguished five sequential stages (referred to as phases) for the evaluation of a complex intervention. These are: pre-clinical theory; Phase I modelling; Phase II

Exploratory trial; Phase III Definitive RCT; and finally; Phase IV long-term implementation. There is a proviso that the phases may not always be sequential, iteration is likely and the framework should be considered in relation to required evidence level and continuum of increasing evidence.[19] The BMJ paper associated with the MRC 2000 framework includes both a linear depiction (Figure 4) and a circular depiction of the framework (Figure 5).[27] The circular depiction is provided to emphasise the iterative nature of intervention development.

In 2006 an independent review was commissioned by the UK government to advise on 'the best design and institutional arrangements for the public funding of health research.' The resultant Cooksey 2006 report [10] presents a linear staged approach to intervention development and identifies two translational gaps: T1 before early clinical trials and T2 before health care delivery.[10] A similar review was commissioned by the US National Institutes of Health. The US report identifies a sequence of research stages and similarly identifies two translational gaps.[28] A third gap (dissemination and implementation research) was added in the 'Blue-Highways' paper by Westfall et al in 2007.[28] In these reports 'gaps' relate to research resource allocation rather than methodology for intervention development.

Despite minor differences the above models all describe staged progression. These stages can essentially be grouped into development, testing, and implementation as summarised in Table 1. A three stage model fails to differentiate summative evaluation points usually described as efficacy, effectiveness and implementation.[21, 26] In staged progression the starting point for effectiveness evaluation is an intervention where efficacy has been proven. The effectiveness problems are then about whether an intervention as it stands is suitable for real world settings and, if not, how it might be redesigned and retested.

The appreciation that health promotion evaluation requirements are different at different stages of intervention development is itself an evolving knowledge base. In their discussion paper about choosing the most appropriate study designs and identifying trade-offs for assessment of effectiveness and other translational research evaluation , Mercer et al (2007) use a comparison chart of research stages that have been identified in linear progression models.[29]

**Figure 4: MRC 2000 framework. Sequential phases of developing randomised trials of complex interventions (Campbell 2000)**

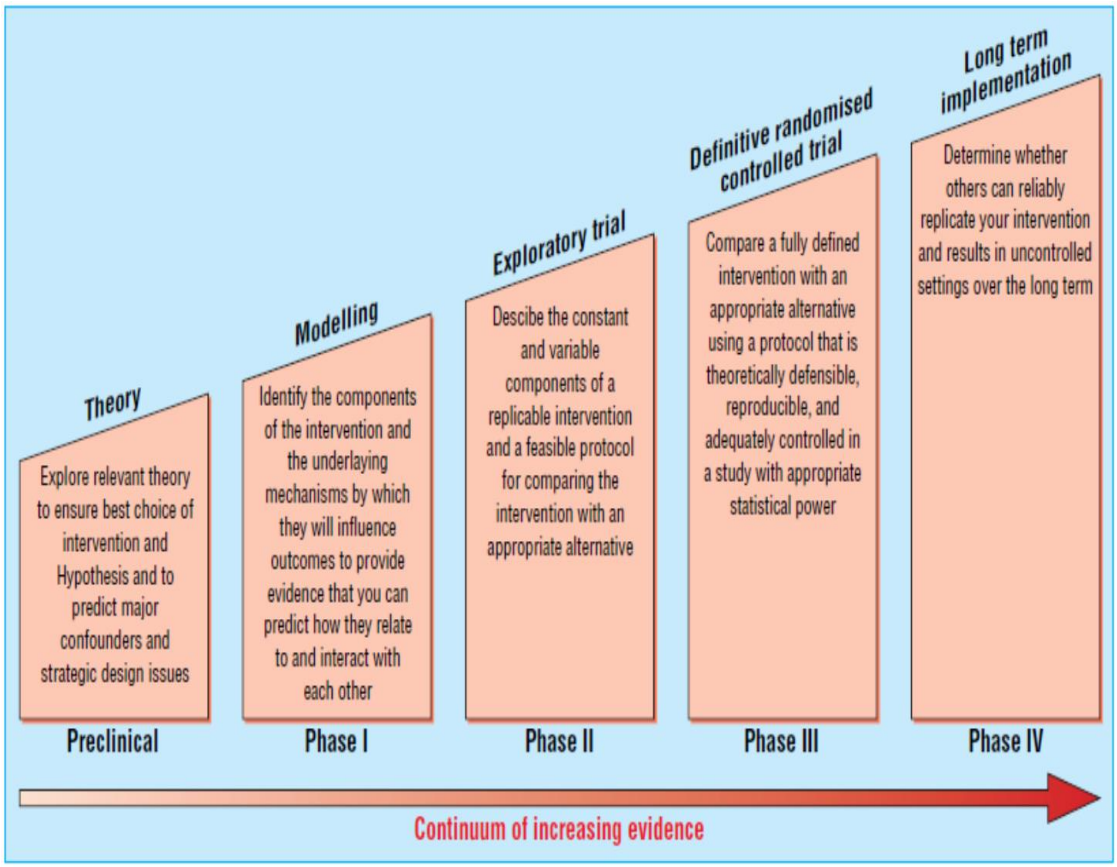
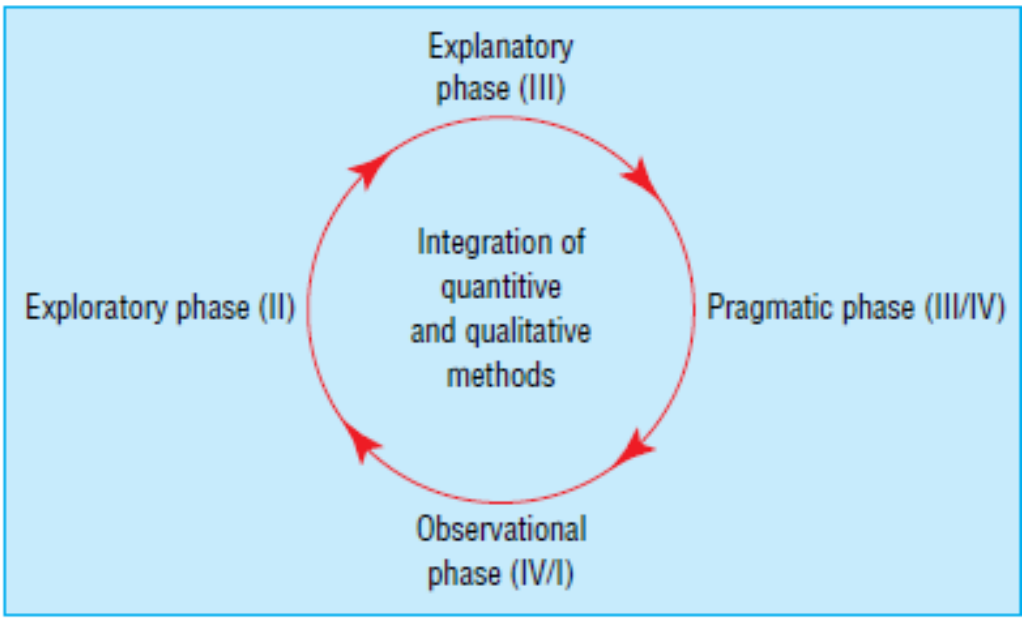



**Figure 5: MRC 2000 framework. Iterative view of the development of randomised controlled trials of complex interventions (Campbell 2000)**



A similar, but more extensive comparison chart of the research stages described in the linear models outlined here is shown in Table 1 below.

By comparing different study designs and identifying trade-offs for evaluation purposes, Mercer et al explain and discuss the inevitable tension between internal and external validity that exists in the design of robust evaluation studies. They also point out difficulties in determining causality and highlight the fact that programme and policy decisions may often be taken irrespective of the availability of robust evidence.

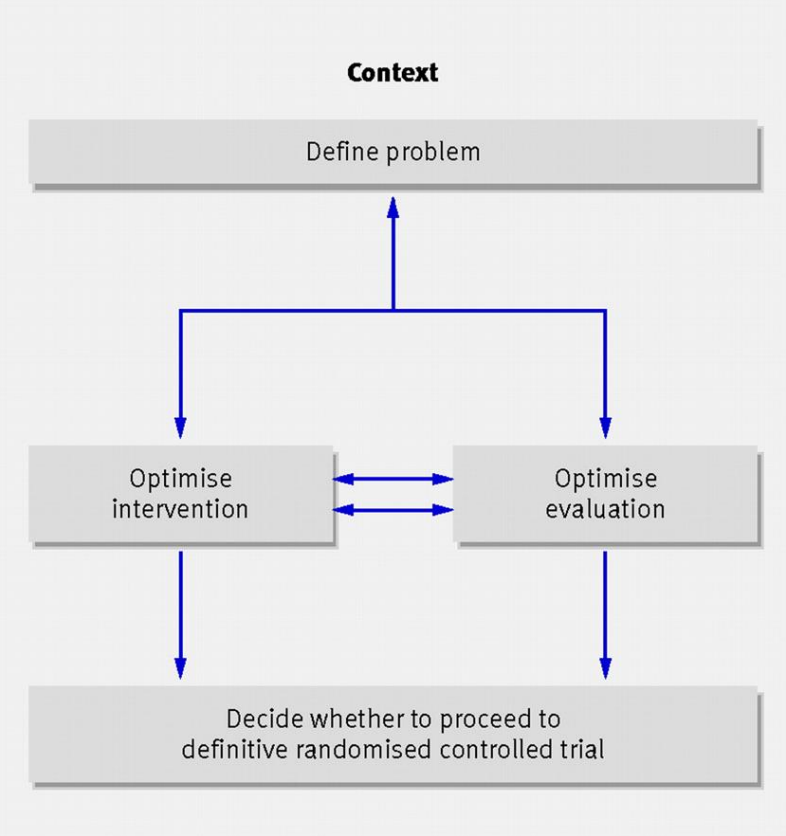
The MRC 2000 guidance [19] was acknowledged as weak on the translation from Phase III, 'definitive RCT' to Phase IV, 'long-term and real-life effectiveness of the intervention'.[10] Limitations of the MRC 2000 guidance were listed in the introduction to the MRC 2008 guidance. There were concerns around the linearity of the clinical trial based model, the limited guidance on implementation phase studies, issues around how to tackle non-health sector interventions, and lack of attention to the intervention context.

In their paper Campbell N et al (2007) discussed the MRC 2000 framework by considering a series of case studies and focussing on pre-trial intervention development. [30] The authors highlighted the MRC 2000 assertion that designing, describing and implementing a well-defined intervention was 'the most challenging part of evaluating a complex intervention and the most frequent weakness in such trials.' The authors also highlighted the need for further framework development. The Campbell N et al 2007 model described two separate, but inter-related strands of activity, 'optimise intervention' and 'optimise evaluation,' that are required in the pre-trial developmental stage (Figure 6). Campbell N et al advocated combining the first three stages (Phases (0, I, II) described in the MRC 2000 framework into one activity with two (intervention and evaluation) strands. They identified several 'key tasks' (centred on: problem definition, population affected, causal pathways, whether amenable to change, and potential for improvement) as necessary pre-trial stage activities. The recommendation that a decision 'whether to proceed to a definitive randomised controlled trial' has to be taken at an early stage is a strength of their work. There is an implication of other stages beyond the advised definitive trial.

**Table 1: Linear progression stages in the development and evaluation of complex interventions to improve health as identified in different models**

| | Development (pre-trial) | | | Trial evaluation | | | Implementation | | |
|---|---|---|---|---|---|---|---|---|---|
| Levy 1982 | 3 stages with one divided into three smaller steps (US National Heart, Lung and Blood Institute Research Spectrum) | | | | | | | | |
| | Basic and clinical research | | | Applied research and development | | | Demonstration and education programs | | |
| | Knowledge acquisition | | | Knowledge validation | | | Knowledge transfer | | |
| | Basic research | | | Applied research | Clinical trials | Prototype studies | Demonstration and education research | | |
| Cullen 1984 | 5 stages (US National Cancer Institute Cancer Control Research Phases) | | | | | | | | |
| | Hypothesis development | Methods development | | Controlled intervention trials | Defined population studies | | Demonstration and implementation | | |
| Flay 1986 | 8 Stages (research pathway) | | | | | | | | |
| | 1Basic research | 2 Hypothesis demonstration | 3 Pilot applied research | 4 prototype evaluation | 5 Efficacy trials | 6 Treatment effectiveness trials | 7 Implementation effectiveness trials | 8 Demonstration evaluations | |
| Nutbeam 1998 | 6 Stages of research and evaluation | | | | | | | | |
| | 1 Problem definition | 2 Solution generation | | 3 Innovation testing | 4 Intervention demonstration | | 5 Dissemination | 6 Programme management | |
| MRC 2000 | 5 Linear stages | | | | | | | | |
| | 0 Theoretical | 1 Modelling | | 2 Exploratory trial | 3 Definitive RCT | | 4 Long term implementation | | |
| Cooksey 2006 | 9 linear stages and 2 translational gaps | | | | | | | | |
| | | | 1st translational gap | | | 2nd translational gap | | | |
| | Basic research | Prototype discovery and design | Preclinical development | Early clinical trials | Late clinical trials | Knowledge management | Health technology assessment | Health services research | Healthcare delivery |

**Figure 6: Relation between context, problem definition, intervention, and evaluation for complex interventions (Campbell N 2007)**



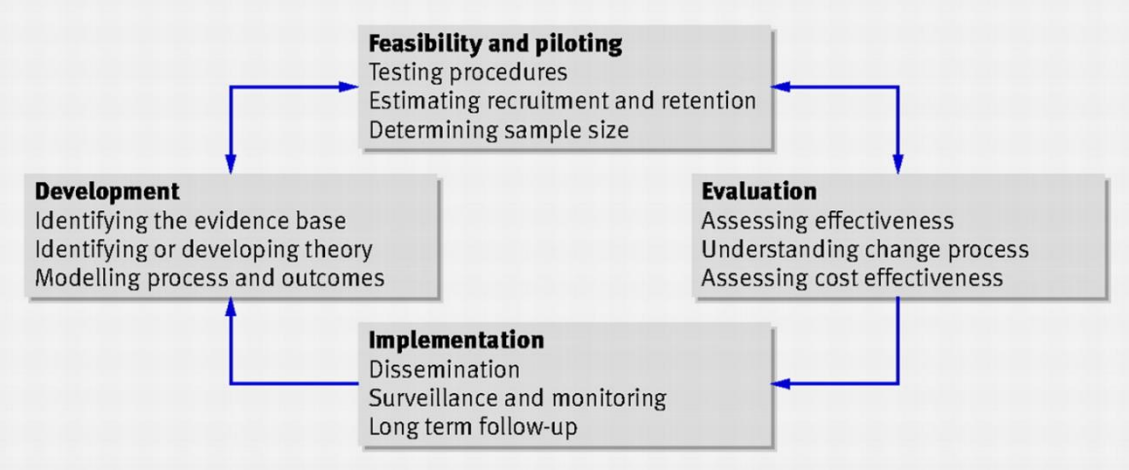

The MRC 2008 guidance built on the MRC 2000 guidance [19] and referenced the work by Campbell N et al. [30] The updated guidance is introduced as providing a, 'more flexible, less linear model of the process, giving due weight to the development and implementation phases as well as to evaluation'. [20] The MRC 2008 framework identified four stages with associated key functions and activities. The four stages are: development; feasibility and piloting; evaluation; and implementation. The MRC 2008 guidance states that these stages may not be linear and should be interactive. This is similar to the approach, for the early pre-trial stage, suggested by Campbell N et al (2007).[30] However, the concept of two parallel strands of 'optimise intervention' and 'optimise evaluation' as discussed in the Campbell model was not included in the MRC 2008 guidance.

Intervention development and evaluation are closely interrelated and might be inextricable in the early stages of intervention development. However, for service provision an intervention needs to exist as an entity, separate from the research

paradigm where it was generated. Clearer distinction between the parallel strands of 'optimise intervention' and 'optimise evaluation' as proposed in the Campbell 2007 model is a useful concept.[30] Failure to address this separation is a limitation of the MRC 2008 guidance. Similarly the concept of different summative evaluation points (efficacy, treatment effectiveness, and implementation effectiveness) evident in earlier sequential models, but not in the MRC 2008 guidance, is a limitation of MRC 2008.

The MRC 2008 guidance [20] is written in three parts: Part I describes four main development and evaluation stages with associated key activities; Part II consists of eleven further questions (that evaluators might usefully ask themselves); and Part III presents a range of case studies. The four stages with their key activities are summarised in Figure 7 below.

**Figure 7: Key elements in the development and evaluation process (MRC 2008)**




Although the iterative nature of the development process is emphasised in the circular depiction of the framework the text is necessarily more sequential in its organisation. It is possible to map the different stages and key elements from MRC 2008 onto the stages as described in MRC 2000 (Table 2).[19, 20] In developing a complex intervention the MRC 2008 guidance includes advice to, 'begin thinking about implementation at an early stage in developing an intervention' with the questions: 'Would it be possible to use this?', 'By whom?', 'In what setting?, Who needs to know about the outcome?' 'What do they need to know?' and, 'What information would be persuasive?' (Page 9) Although implementation to improve population health is the ultimate purpose

**Table 2: Key-elements identified in the MRC 2008 framework mapped to the linear progression stages in the MRC 2000 framework**

| MRC 2000<br>5 Linear stages (Phases) | | | | |
|---|---|---|---|---|
| 0 Theoretical | 1 Modelling | 2 Exploratory trial | 3 Definitive RCT | 4 Long term implementation |
| MRC 2008<br>Four iterative stages with associated key elements | | | | |
| **Development**<br>Identifying the evidence base<br>Identifying or developing theory<br>Modelling process and outcomes | **Feasibility and piloting**<br>Testing procedures<br>Estimating recruitment and retention<br>Determining sample size | **Evaluation**<br>Assessing effectiveness<br>Understanding change processes<br>Assessing cost effectiveness | | **Implementation**<br>Dissemination<br>Surveillance and monitoring<br>Long term follow-up |

behind intervention development, the fundamentally important prior requirement to demonstrate intervention efficacy (Does it achieve the primary outcome of interest under optimal conditions?), which is made clear in early models of intervention development has been lost in the MRC 2008 framework. There is a danger that by overloading early efficacy evaluation with excessive outcome and process data-collection the opportunity to assess an optimal intervention could be buried beneath excessive respondent burden. Thus the opportunity to answer to the important question 'Does it achieve the primary outcome of interest under optimal conditions?' is lost. The need to avoid excessive respondent burden and a need to, 'Keep it simple' in designing interventions should be acknowledged in any guidance model.[31]

The iterative development concept in MRC 2008 guidance means that differences in the outcomes that are of most relevance and value at different stages, cannot be teased out. For example evaluation of cost-effectiveness might be less relevant in early stages of intervention development, when the emphasis should be on whether the intervention will achieve the primary outcome of interest irrespective of detailed cost and benefit comparisons. That said there is an argument for modelling likely cost and benefit to avoid wasting resources on an impossibly high cost intervention of limited benefit.

In structuring the framework around four key elements the MRC 2008 guidance draws an apparently simple model. However, the essence of simplicity requires sufficiently clear building blocks such that communication and interpretation are likely to have consistency. A model based on interaction of key elements and iteration is unlikely to achieve this. Where to start and progression order is important in any design project, and intervention design is not fundamentally different in this respect. The three part layout of the MRC 2008 guidance (Key messages (including Key elements), further questions, case studies), together with additional explanatory text boxes, adds further complexity to the guidance that makes it difficult to ensure comprehensive absorption of all relevant information, and thus provides opportunity for variation in interpretation.

## 2.3 The sociological research perspective

A different approach to design and evaluation of complex interventions was introduced by Glasgow et al in the RE-AIM framework(1999).[32] The focus described in

the RE-AIM framework was on translation of research into practice, emphasising: 'The reach and representativeness of both participants and settings' (page 1322).[32] This alternative focus was derived from sociological research roots rather than the biomedical perspective of the models described above. The RE-AIM authors addressed the need to focus on the overarching aim of population based impact of interventions and the importance of embedding interventions in host organisations with consideration of fidelity of intervention delivery and sustainability. RE-AIM uses the evaluation dimensions: Reach into the target population (with reference to the inclusion of diverse patient groups); Efficacy or effectiveness; Adoption by target clinicians and practice settings or institutions; and IMplementation. Implementation is specifically defined in this framework as comprising consistency of intervention delivery and maintenance of intervention effects in individuals and populations over time.

Some of the evaluation dimensions in the RE-AIM framework can be mapped to research stages described in previous linear phased models described above, whilst others cannot. This raises questions around classification and highlights a need for consistent terminology to avoid confusion and promote effective communication. For example 'reach' cannot be described as an evaluation stage (and is unlikely to be confused in this respect), and 'implementation' is used to mean different things in different models.

The RE-AIM framework[32] was reviewed along with other models important to implementing evidence based practice including the Diffusion of Innovations, [33] The Chronic Care model[34] and Model for improvement.[35] These models were assimilated to develop the Practical, Robust Implementation and Sustainability (PRISM) model in 2008.[36] In developing the PRISM model the authors sought to address issues of implementation, 'outside the research study.' They make the point that, 'As long as efficacy and effectiveness trials are considered complete,' [without implementation] their potentials are not realised. The PRISM model aims to identify measures to support evaluation around how an intervention or health care programme interacts with its recipients and the influences of this interaction on implementation. Relative advantage of adopting new behaviours, from the perspectives of intervention recipients, is an important concept in the model alongside ensuring cultural

acceptability of the intervention, fit with the environmental context and adaptability to local settings. Activities to support implementation include: creating an infrastructure to encourage the spread of the intervention; addressing the barriers of frontline staff; linkage with service providers and users in the design stages; and leveraging community support. The outcome measures originating from the RE-AIM framework are incorporated into PRISM with the need for usefully formatted feedback reports to facilitate adjustments. PRISM is supported by case studies that highlight elements shown to affect intervention implementation and sustainability.[36]

A conceptual model of determinants of diffusion of innovations in service organisations was derived from a systematic review and evidence synthesis of empirical studies by Greenhalgh et al (2004).[37] In this paper the concept of 'relative advantage' is described as a *'sine qua non'* for innovation adoption by potential users. This mirrors the identification of this important concept in the PRISM model. The Greenhalgh et al model identifies linked 'resource' and 'user' systems. The authors include a list of 'innovation attributes' that predict adoption of an innovation and 'system antecedents' that affect implementation. Communication diffusion and dissemination pathways are included in this model.

The focus of the Greenhalgh et al paper is on diffusion of innovations in health care organisations. Importantly the authors highlight the paucity of evidence around sustainability of innovations and suggest various areas for empirical research around implementing and maintaining innovations. Linkage with potential users at the development stage is echoed in the Greenhalgh model and described as a key activity that includes a concept of shared intervention development.

The Normalization Process Model (NPM) proposed by May et al 2007 seeks to 'Assist in explaining processes by which complex interventions become routinely embedded in health care practice.' [38] The model identifies four influential factors: interactional workability, relational integration, skill-set workability, and contextual integration, which affect implementation of interventions. The NPM draws on sociological research around collective social action or group processes in the context of health care organisations and is principally about the behaviours of health care professionals. Normalization is defined as referring to the routine embedding of an innovation and is contrasted with 'adoption' where an innovation is taken up, but does not become

routinely embedded and 'rejection' where an intervention is refused (not taken up). The concept of 'adoption' in this model is therefore different from that described in the PRISM model. Normalization appears to be broadly equivalent to routinization in the Greenhalgh model. All three models, (Prism, Greenhalgh, and NPM) derive from a social science perspective.

For public health interventions, implementation within a health care organisation is too narrow a focus and does not address potential for intervention providers to be different organisations, including community based organisations. Nor does the narrow focus on health services address the potential for collateral public health impact of interventions that are instigated primarily for other purposes.

Some evaluation models derived from a social science discipline have broader perspectives, beyond implementation in health care. Realist evaluation as described by Pawson and Tilley [39] asserts that social programmes are 'hypotheses about social betterment,' or a 'vision of change,' thus programmes, 'succeed or fail depending on the veracity of that vision.' Pawson and Tilley describe evaluation as hypothesis testing that involves: formulating a hypothesis; collecting data on 'appropriate mechanisms, contexts and outcomes;' analysis of the data in relation to 'outcome patterns to see which can and which cannot be explained by initial theory;' and finally testing and refining the theory. All of which is a prelude to the next round of ' theory refinement.'[39] How a programme might work in this model is viewed as a function of intervention design and its application. A distinction is made by Pawson and Tilley between formative and summative process evaluations. Thinking through different aspect s of a problem, formulating and refining plausible mechanisms for preventive initiatives accords with a realist approach to formative process evaluation. Collecting data to analyse how outcome patterns may be explained by different mechanisms in relation to different contexts accords with a realist approach to summative process evaluation.

Process evaluation and theory testing have value in informing intervention design. However in interventions that are designed to improve health, the primary outcome is often a simple, robust and science based, health related or clinical measure. This outcome is beyond theory testing. What is meant by whether a programme 'works' depends on how the outcomes of interest are defined.

Implementation fidelity in community based interventions is addressed in a paper by Breitenstein et al (2010).[23] Terminology is well defined in this paper with fidelity described as, 'an intervention being delivered as intended by the programme developers and in line with the programme model.' The authors describe two components of fidelity: adherence and competence. Adherence measures are of components specific and essential to an intervention, whereas competence relates to how well an intervention is delivered. Competence includes assessment of capabilities and skills of delivery staff. Staff selection, training, coaching, and supervision contribute to competence and hence to fidelity. The authors advocate clear strategies for fidelity monitoring and discuss available options. The tension between prescriptive intervention protocols and flexibility in protocol design to allow consideration of context and responsivity by trained delivery staff is discussed. The authors point out that the relationship between fidelity measures and outcome measures is under researched and unclear.

## 2.4 Models that have a specific focus

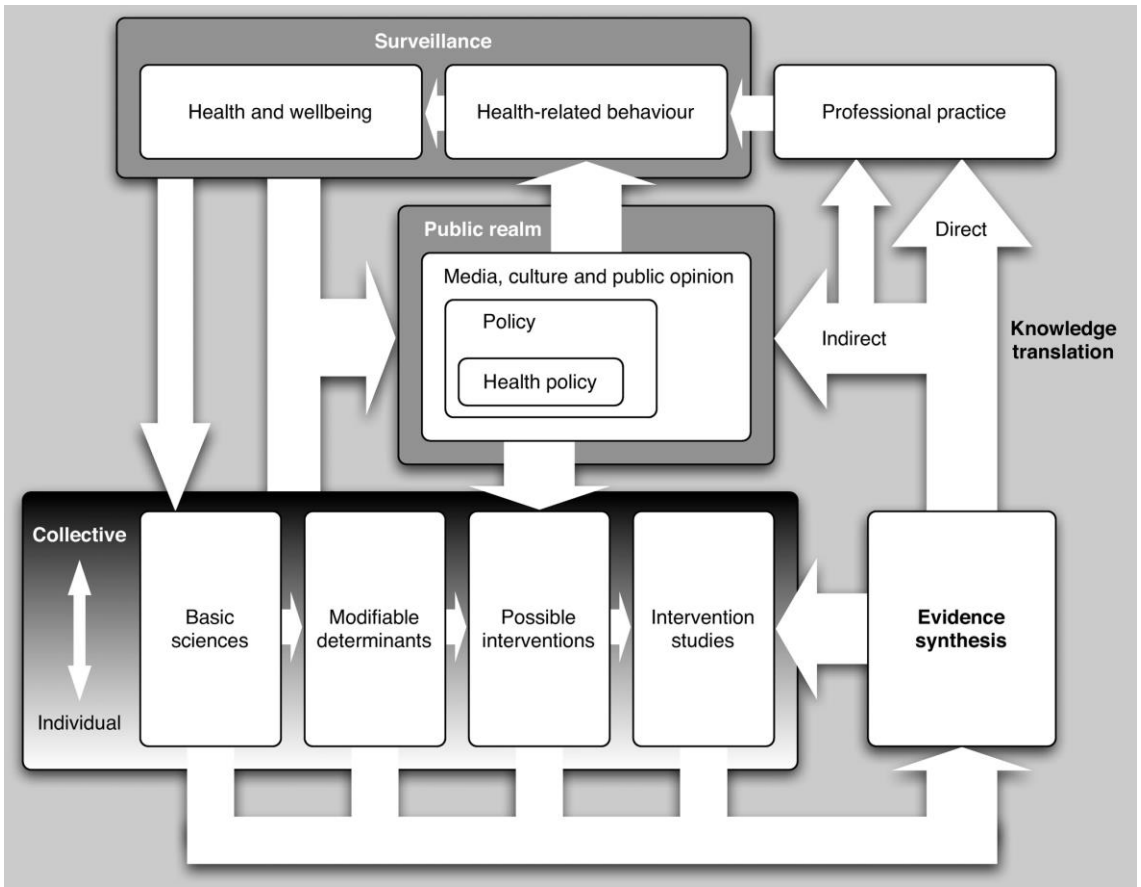
Work by Collins et al (2004) introduces the idea of adaptive preventive interventions and tailoring variables, such that the 'dose' of an intervention would vary with individual needs. This individual approach may not always be possible. The broader idea that intervention provision needs to be culturally acceptable is practical, and included in the PRISM model.[36] The idea that a health promotion intervention could be culturally adapted has more recently been explored in an extensive Health Technology Assessment report.[40]

Ogilvie et al (2009) proposed the 'Translational framework for public health research'[41] that introduces a public realm 'hub' of media, culture, opinion, and policy. This framework clarifies the domain of public health as extending beyond a narrow focus on established systems of health care delivery. The endpoint of intervention is defined as improving population health. This public health domain is expanded in the UK Government commissioned Acheson Report as 'The science and art of preventing disease, prolonging life and promoting health through organised efforts of society.' [42] The Acheson report references work from the nineteen twenties.[43] However, linking population health improvement to a specific intervention provision can be problematic.

The development of this Translational framework model draws on earlier models, including the translational pathway in the Cooksey report.[10] However, the authors suggest that the remit of translational public health research to be concerned with implementation of 'proven' interventions (as described in the US Centres for Disease Control and Prevention (CDC) roadmaps),[28] is too narrow. Ogilvie et al stress the importance of epidemiology and the inclusion of an expanded and pivotal role for evidence synthesis that is not restricted to RCT evidence is a strength of this model. The authors also note different intervention and outcome levels (individual and societal) as previously described in the Nutbeam model.[44]

The diagrammatic depiction of the framework is provided in a circular format shown in Figure 8 below. [41] This diagram is complex and arguably less amenable to consistent interpretation than simpler linear models. The lack of detail around intervention studies limits utility for intervention design, although it should be recognised that intervention design is not the main purpose of this model.

**Figure 8: Translational framework for public health research (Ogilvie 2009)**



An ‘Evolutionary flowchart for typical complex public health interventions’ is included within the paper on ‘Evaluability of complex interventions’ by Ogilvie et al (2011).[22] The main focus of this paper is on five questions to assess evaluability. A further stated aim of this model is to, ‘better reflect the wider socio-political context in which complex public health interventions take place,’ thus extending the scope of evaluation beyond a narrow health care focus and reflecting the ‘broader focus’ previously explained by Ogilvie et al in 2009. The extended vocabulary of implementation with broader themes including generalisability and scalability is a particular strength of this model. The evolutionary flowchart is shown in Figure 9 below.

A paradigm of circles or loops within a larger framework is clearly evident in the flowchart depiction. This model retains the concept of stages as envisaged in early linear models and uses the term ‘evolutionary’ to describe this staged progression. The idea of ‘key evaluable constructs’ that are particularly applicable to different evolutionary stages is introduced. Different outcome levels (individual, group, community and population) and different outcome domains (intention, behaviour, adiposity, health etc.) expand on the ‘valued outcomes,’ described by Nutbeam in 1998.[21] Interestingly the separation of ‘intervention’ (white boxes) and ‘key evaluable constructs’ (shaded boxes) as suggested by Campbell N (2007)[30] is evident in this new framework. The distinction between process and outcome evaluation, which is a recurrent theme in other models, is expanded in this model. These aspects contribute to the utility of this evolutionary flow chart for application to intervention development and evaluation (although this is not the main purpose of the paper).

The paper focusses on five questions to assess evaluability. The first question asks where the intervention is situated in the evolutionary flowchart of an overall intervention programme. However, it is not entirely clear from the example given why assessment of barriers and facilitators to intervention participation should precede evaluation of plausible health related outcomes. The second question is about the need to consider the effect of evaluation on policy decisions. However, this consideration of policy is qualified by the authors who highlight the undesirability of

being, ‘shackled to an excessively instrumental or pragmatic view of the value of research,’ thus this question is perhaps misleading at first glance.

The third question is about possible impact of evaluation and includes reference to the relevance of plausible mechanisms. I suggest that, ‘Is there a plausible mechanism for the intervention?’ should be a key evaluability question in its own right. The starting point of the flow chart (concept, idea, or policy proposal) includes no explicit relation to scientific, aetiological or epidemiological, evolutionary roots. Thus, it is not clear how or where the concept, idea or policy proposal might have arisen. Epidemiology and knowledge of disease aetiology contribute to evaluability by providing a firm foundation on which intervention development and evaluation can be built.[45]

The fourth evaluability question, which is about whether the evaluation would add value to existing scientific evidence, supports the suggestion that a scientific foundation for intervention development would be relevant to evaluability. The final question is about time constraints for the conduct of an evaluation. This is an important evaluability question that reflects the tension between a need to ‘press on’ with intervention delivery at the expense of considered evaluation.[46]

The evolutionary flowchart includes the concept of a ‘concrete’ developed intervention. Whereas it is true that an intervention needs to be defined precisely, for example in a trial protocol, for the purposes of robust evaluation, it is also true that an intervention is unlikely to be translated to multiple contexts without some modifications. For the purpose of controlled outcome evaluation a fairly precise, and protocol or agreement defined intervention, and a pause in intervention development applied at any of the evolutionary stages, might be necessary.

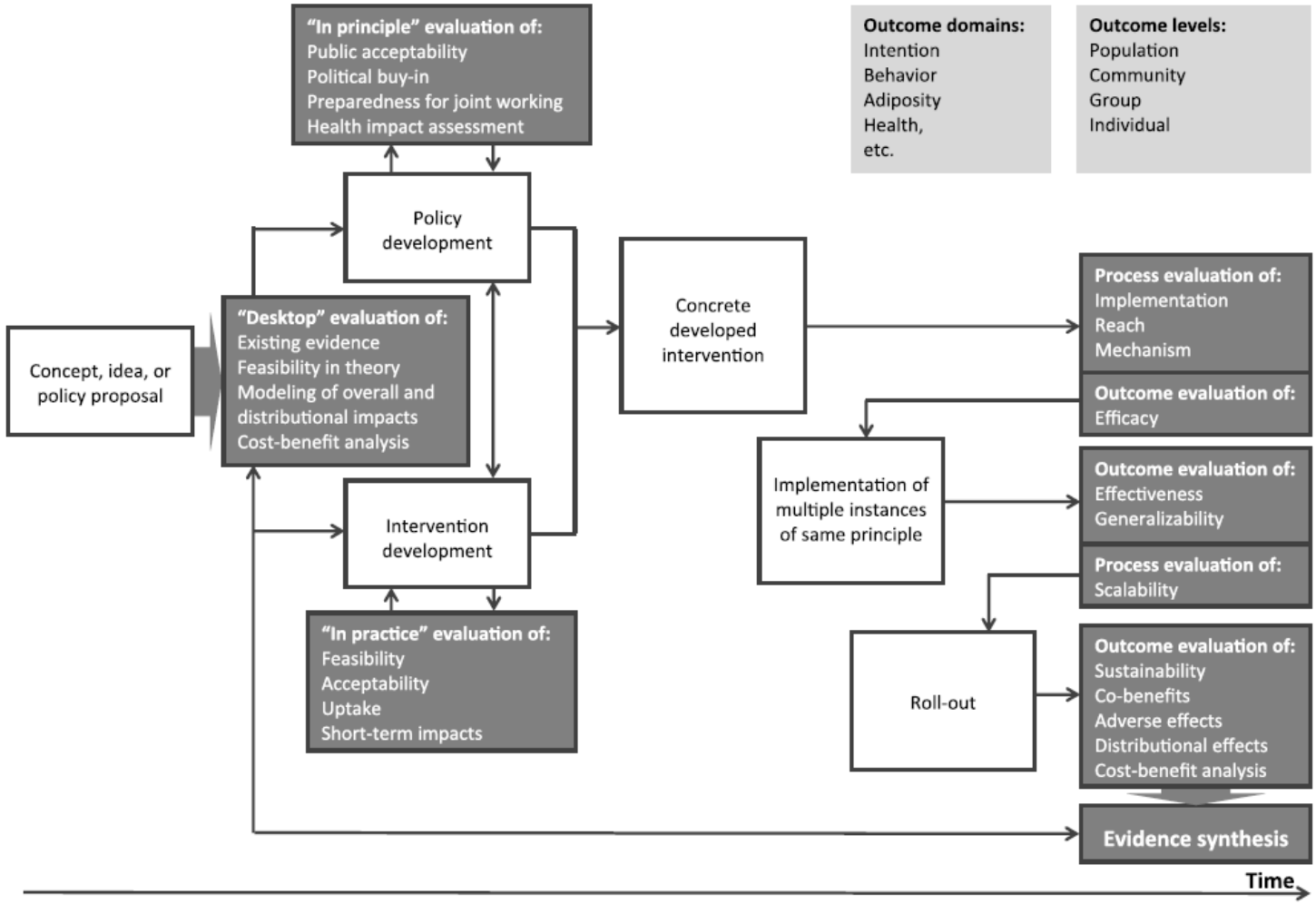
Although the Ogilvie et al 2011 model is described as a flowchart it does not use standard flowchart decision boxes. Conventionally flowchart decision boxes are diamond shaped. Using a decision diamond allows one input to be related to three outputs. In the case of evolutionary stages of intervention development the decisions at each stage are dependent on the success or otherwise of the evaluation in achieving the outcomes of interest. Appropriate decisions might be either: proceed to the next stage; return to a previous stage for further intervention refinement; or do not proceed further.

It is surprising that of all these framework depictions only 'Levy's arrow' employs a visual metaphor. [24] Metaphors can aid memorable communication in serving to organise and structure complex information.[47] In addition, a good visual metaphor can convey an implicit insight by drawing on meaningful characteristics or associations that relate the metaphor to the information. Describing the staged approach to intervention development and evaluation as 'evolutionary' in the evolutionary flowchart model introduces an implied metaphor (although not visually).

## 2.5 Principal findings

In this review of guidance for the development and evaluation of complex interventions to improve health, I have identified two main early approaches to guideline development: bio-medical and sociological. The strengths of the bio-medical based linear continuum approach include clearly defined evolutionary stages that proceed from an aetiological and epidemiological scientific base where evaluation is centred on a clearly identified health related primary outcome. This approach has been limited by a focus on early intervention development stages, prior to formal testing, such as in a trial (efficacy), and insufficient elaboration around translation of trial evidence to real world settings or implementation of interventions as service provisions. In contrast the sociological approaches centre on theories relating to implementation.[37, 38] Implementation in health care organisations is too narrow for public health interventions that may be community based, commissioned services, or multi-sectorial. Other guidance model approaches have been more purpose focussed, for example on adaptation or evaluability of interventions. Process evaluation is important,[48] but outcome measures provide a robust evidence base for service provision.

**Figure 9: Evolutionary flowchart for typical complex public health interventions**




Open boxes represent different stages in the evolution of an intervention. Shaded boxes summarize key evaluable constructs at different stages. Constructs listed down right-hand side could all apply to all stages from "concrete" to "roll-out," but the likelihood of being able to measure the items lower down the list, or generalize from the observations, increases as implementation proceeds from "concrete" through "multiple instances" to "roll-out" (Nutbeam 1998).

Separation of intervention development and evaluation strands, an appreciation of the difference between formative and summative evaluation, and the need for defined outcome measures set the scene to clarify the evolutionary summative evaluation points. These main summative evaluation points have been described as: efficacy (trial of an optimal intervention in ideal circumstances); effectiveness (trial of an implementable intervention in real world settings); implementation (evaluation of routine delivery). Further evaluation points of sustainability and population health impact are also relevant. I suggest that the tension between sequential and iterative approaches highlighted in the MRC frameworks and depicted in these and subsequent frameworks by using a single, circular format with bi-directional arrows, leads to confusion that could limit the efficient development of effective and sustainable public health interventions.

However, the 'key functions and activities' of intervention development as listed in the MRC 2008 framework have provided useful detailed guidance for intervention development. These activities and other intervention development activities could be variously applicable prior to any of the summative evaluation points outlined above. Sequential staged evaluation points are necessarily progressive, but the processes of intervention development prior to efficacy evaluation, or prior to effectiveness evaluation have commonalities as well as differences.

The focus in this thesis is on evidence based interventions specifically intended for health improvement. It should be remembered that public health policy can be implemented without good supporting evidence[46] and collateral health benefits can arise from policy initiatives in other sectors. However, the link between intervention and its effect can be difficult to determine in these situations, which limits systematic intervention development and is beyond the scope of this thesis.

## 2.6 Type 2 diabetes as a case study to support guideline development

The case of T2D in relation to research model development was proposed by Narayan in 2004.[49] In Narayan's paper, the extension of 'effectiveness to translational research' is explained as a broader paradigm that includes sustainability, generalisability and transferability to the majority of people and to diverse settings. Narayan advocates the establishment of large multicentre studies for translation of research and introduces the public health orientation of optimal health care for many, within constraints of

cost, capacity and equity. In this model there is little detailed consideration of intervention development.

Case studies have been used to support proposed guidance frameworks and analysis of T2D prevention has unique utility as a case study for this purpose. In the next chapter I describe T2D, its diagnosis, prevalence, aetiology, and associated sub-clinical conditions, prior to reviewing the empirical evidence for T2D prevention in individuals at high-risk.

# CHAPTER THREE: TYPE 2 DIABETES

## 3.1 Prevalence and epidemiology, increasing incidence and importance to world health

Type 2 diabetes is a disease of impaired metabolism of carbohydrate, fat, and protein that results in hyperglycaemia.[50] The prevalence of diabetes is increasing worldwide and it is expected to affect 438 million people by 2030.[51] Diabetes is therefore a major world health problem. Type 2 diabetes accounts for 85% to 95% of diabetes in high income countries where it is now affecting increasingly younger and working-age adults with adverse impacts on: their life expectancy and quality of life, the duration and economic burden of their care, and economic productivity of their countries.[51] There is a genetic predisposition for T2D: people who have a first degree family member (father, mother, brother, or sister) with T2D have a five to ten times greater lifetime risk compared with a person with no family history.[52] Presence of T2D associated genes and their interactions contribute to an individual's risk profile.[4] Also the likelihood of developing T2D is greater in certain ethnic groups, such as people of South Asian and African descent.[53] However, T2D is essentially a lifestyle disease, which is associated with obesity, inactivity, unhealthy diet, urban living, and increasing age. [54, 55] It is a debilitating and progressive disease with specific vascular complications. Microvascular diseases associated with diabetes include: retinopathy, a disease of the eye retina that can progress from mild to proliferative retinopathy and may result in blindness; neuropathy, a kidney disease that can lead to kidney failure: and nephropathy, a nerve disease that can result in ulcerations, particularly of the lower limbs that may result in amputations. Diabetes is also associated with an increased risk of cardiovascular disease (coronary heart disease and stroke) and premature death.[56] Diabetic complications are more likely to progress where blood glucose levels are poorly controlled. Diabetes related treatment cost to the NHS are currently estimated to be almost 8 billion per year and these are expected to rise to over 15 billion by 2035 in line with increasing diabetes prevalence.[57]

## 3.2 Aetiology and diagnosis

In type 2 diabetes the raised blood glucose is caused by insufficient insulin secretion, resistance to insulin action in the body tissues, principally muscle and liver tissues, or a

combination of both defects.[50 58] In the early stages T2D is often asymptomatic and can remain undetected for years. Type 2 diabetes is diagnosed when hyperglycaemia reaches a level that is associated with particularly increased risk of adverse pathological changes (usually referred to as 'complications'). This level is somewhat arbitrary and represents a cut-point on a continuous scale. The cut-point used clinically has changed over time as a result of changing knowledge of the epidemiology of the disease and its outcomes. The trend has been towards a lower cut-point over time, resulting in diagnosis at an earlier stage of disease progression, which is likely to reduce complications and thus improve outcomes overall. [59]

The cut-points to diagnose T2D are determined from glycaemia values as surrogate biomarkers for the prediction of prevalent retinopathy. These cut-point values, agreed by an expert committee, were first published by World Health Organization (WHO) in 1965,[60] and revised in 1999.[61] The WHO 1999 report includes diagnosis and classification of T2D based on two plasma glucose values: either fasting plasma glucose (FPG) or plasma glucose at two hours (2hrPG) following a standard oral glucose tolerance test (OGTT). [59] A standard OGTT involves ingestion of 75 grams anhydrous weight of glucose, usually as a glucose drink, following a fast of 10 to 12 hours. Blood is then drawn from the anti-cubital vein after two hours with very limited activity. The WHO 1999 diagnostic values are: FPG ≥ 7.0 mmol/l, and 2hrPG of ≥11.1 mmol/l (OGTT). Both these blood tests require a fasting test (usually self-reported) and may be affected by medication, test processing quality and non-adherence to fast.

In 2011 the guidance for diagnosis of type 2 diabetes was reviewed by WHO and updated to include diagnosis based on the venous blood level of glycated haemoglobin (HbA1c).[62] This type of haemoglobin provides a measure of the plasma glucose values over the previous eight to twelve weeks and is higher in those with hyperglycaemia. Diagnostic HbA1c cut-points were based on epidemiological studies of retinopathy in relation to HbA1c (rather than comparison with other parameters such as 2hrPG). The prediction of prevalent retinopathy is similar for all three glycaemia measures, although the optimal cut-points vary between studies.[63] As a diagnostic criterion HbA1c has the advantage of convenience for patients as no fast is required, but it is affected by some haemoglobin related conditions and is not available in all countries. Where conditions are suitable, HbA1c has been recommended for diabetes diagnosis

by both WHO and the American Diabetes Association (ADA). If the HbA1c level is ≥ 48 mmol/mol (International Federation of Clinical Chemistry (IFCC) measure, which is equivalent to the Diabetes Control and Complications Trial (DCCT) measure of 6.5%).[64] In the absence of clinical symptoms, diabetes diagnosis should be confirmed with a repeat test (Fasting Plasma Glucose (FPG, 2hrPG, or HbA1c), between one to twelve weeks later, preferably using the same measure.[63]

Other diabetes classifications can be confused with T2D. Blood glucose tests alone will not differentiate between T2D and Latent Auto-immune Diabetes in Adults (LADA) or Maturity-Onset Diabetes of the Young (MODY).[61] The distinction is important for appropriate treatment and there may be further sub-classifications as yet imperfectly determined or described.

### 3.3 Risk factors and sub-clinical conditions

Knowledge of the progressive metabolic defects preceding T2D has led to the identification of two WHO defined non-diabetic hyperglycaemic conditions: impaired fasting glucose (IFG), which is defined by WHO as a fasting plasma glucose ≥ 6.1 and < 7.0 mmol/l (ADA ≥ 5.6 and <7.0 mmol/l), and impaired glucose tolerance (IGT), which is defined, by both WHO and ADA, as fasting plasma glucose < 7.0 mmol/l and two hour plasma glucose ≥7.8 mmol/l and <11.1 mmol/l (FPG < 7.0 mmol/l if measured) following a standard OGTT.[61]

### 3.4 Diagnostic criteria

The criteria for diagnosis of T2D and criteria for related hyperglycaemic conditions are summarised in Table 3. If untreated, around 50% of people with IGT will progress to T2D within 10 years.[65] Other risk factors for T2D are associated with IGT including central obesity and dislipidaemia and IGT is a risk predictor of cardiovascular disease (independent of overt T2D).[66] Reports of the progression from IFG to T2D are variable and mostly based on the earlier WHO 1985 and ADA criterion of FPG ≥ 7.8 mmol/l for diagnosis of T2D. [67, 68]

A number of risk scores, based on simple measures (such as family history of T2D and body mass index(BMI)), have been devised using cross-sectional data to screen for T2D prevalence.[69] In addition several prospective risk scores have been devised using multivariate regression applied to risk parameters in cohort study data to predict

future development of T2D (incident T2D).[70 71] One example of a prospective risk-predictor is the Finnish diabetes risk score, FINDRISC. This risk calculator uses simple non-invasive measures.[72] The FINDRISC parameters are presented as categorical variables (with continuous variables grouped in categories where necessary), which means that this risk calculator can be simply completed and the risk score calculated as a paper exercise.

**TABLE 3: Diagnosis of diabetes mellitus and other categories of hyperglycaemia**

Modified from the WHO Consultation Report: Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications, 1999 [61]

| | Plasma venous glucose [a] mmol/L (mg/dl) |
|---|---|
| **Diabetes mellitus:** | |
| Fasting | ≥7.0 (126) |
| 2-hour post-glucose load | ≥11.1 (200) |
| **Impaired glucose tolerance (IGT):** | |
| Fasting (if measured) | < 7.0 (126) |
| 2-hour post-glucose load | 7.8–11.0 (140–199) |
| **Impaired fasting glycaemia (IFG):** | |
| Fasting | 5.6–6.9 (100–125) |
| 2-hours (if measured) | < 7.8 (140) |

a Corresponding values for capillary plasma differ only for the 2-hour values: for diabetes, 2 hours≥ 12.2 mmol/L (> 220 mg/dl); for IGT, 2 hours≥ 8.9 mmol/L (≥ 160 mg/dl) and < 12.2 mmol/L (< 220 mg/dl).

Recently, in the UK, a prospective T2D risk score: QDiabetes, that uses parameters routinely available in primary care, has been developed.[73] This risk calculator uses categorical variables and continuous variables as appropriate and is available as an on-line calculator. QDiabetes includes parameters for ethnicity and socio-economic status as well as for smoking status (these parameters are not included in FINDRISC), but does not include waist circumference as this is not routinely collected UK data.[71] Higher scores within prospective risk assessments may also identify prevalent T2D, where this is present, with varying sensitivity and specificity depending on the particular risk score and its parameters. Risk scores are population specific. This means

that a risk score that has been developed in one population cannot be assumed to be valid in another population. However, the progression rates from IFG and IGT to T2D are similarly population specific, so the determination of an individual's risk of developing T2D can only be predicted with a reasonable degree of accuracy when suitably comparable population cohort data are available.[50]

## 3.5 Inequality and distribution of risk factors

The rate of conversion from dysglycaemia to T2D is different in different population groups. People of African-Caribbean and South Asian origin have a higher risk of progression and prevalence of T2D is greater in these ethnic groups.[74] Prevalence of T2D is also socio-economically patterned.[75, 76]

## 3.6 Diagnosis and 'metabolic' reversal

Type 2 diabetes is diagnosed on the basis of sustained hyperglycaemia (with or without clinical symptoms) as a surrogate biomarker for microvascular and macrovascular risk. Therefore, T2D may be diagnosed in the absence of overt complications.[61] Recent work has shown that, at least in the early years post diagnosis, the metabolic effects of T2D can be reversed by application of extreme dietary restriction, which may be associated with bariatric surgery.[58]

Consideration of both the potential for metabolic reversal of T2D and the sub-clinical conditions (IGT and IFG) has led to a greater understanding of the disease pathogenesis.[77] Where people have an inherited susceptibility to T2D, excess calorie intake and inactivity leads to insulin resistance in muscle tissue. The increased insulin secretion thus required to maintain glucose homeostasis facilitates deposition of fat in the liver. This 'fatty liver' condition causes raised plasma triglycerides and fatty-acids. Hyper-lipidaemia affects the pancreatic beta-cells causing cell dysfunction and reduced capacity for insulin secretion. The consequent inability to maintain glucose homeostasis and resultant hyperglycaemia, so called glucotoxicity, similarly affects the function of the pancreatic beta-cells. As long as the beta-cell function is recoverable, in the early pathogenesis of T2D, the disease may be reversed. Continued glucose and lipid toxicity eventually results in irreversible beta-cell damage and eventually cell death.

Liver fat is mobilised early under conditions of dietary restriction (i.e. negative energy balance). Consequently, extreme dietary restriction can have dramatic, almost immediate effects on the disease causing 'metabolic reversal' which may be permanent with continued dietary restraint. Reversing a clinical diagnosis may be problematic, however. The idea of intervention for disease reversal is still at an early stage, but it is entirely logical when the disease diagnosis rests on defined cut-points on a continuum of blood glucose values. Indeed, as the cut-points are defined using three different measures of blood glucose with or without repeat measures and/or clinical symptoms, there is necessarily some uncertainty around accurate diagnosis. However, the benefit of screening, early detection of T2D and intervention aimed at reduction in mortality has not been proven. [78] The development of interventions for primary prevention of T2D is much more advanced.

## 3.7 Public health and UK context

There is strong evidence for the effectiveness of lifestyle interventions to prevent or delay the onset of T2D in high risk individuals.[6] The challenge is to use this research evidence to develop feasible, cost-effective, and sustainable interventions suitable for service provision. Some countries have already implemented large-scale prevention programmes, with various associated evaluation procedures, but the UK has only recently developed nationally agreed guidance. The National Institute for Health and Care Excellence (NICE) convened Programme Development Groups (PDG) to develop guidance for T2D prevention strategies for England.[79] [80]

The 2010 National Health Service UK (NHS) white paper describes the reorganisation of Public Health.[81] Health Improvement is now sited within local government, where the local authority and their director of public health have responsibility for a budget (which is currently ring-fenced) that should be spent to improve health and well-being of the local population. Health and well-being boards, consisting of NHS commissioners, locally elected councillors, and patient champions, are convened to steer the public health agenda, as well as social care, children's services and the wider work of the NHS.

These changes in the organisation of public health services in England and the NICE guidance provide an opportunity for prevention of T2D in England to be developed as a service provision, out-with the usual clinical care pathway. For example local authority

leisure services may already be delivering weight management programmes and exercise on referral programmes. Adaptations in the design and application of these programmes, within leisure services, could be used to deliver lifestyle interventions more specifically targeted to defined outcomes including prevention of type 2 diabetes. As general practices are already overstretched, the opportunity to utilise local authority leisure services or similar providers to deliver preventive interventions may be an attractive option for NHS commissioners. The challenge is to design commissionable services that are accountable, with relevant and robust outcome measures.

The NHS Health Checks programme is a service for assessment of cardiovascular disease (CVD) risk. [82] Many of the risk variables for CVD are also T2D risk variables. Prospective risk scores to identify individual risk of CVD are available. The most commonly used CVD risk scores in the UK are the Framingham risk score[83] and QRisk.[84] [85] The NHS Health Checks programme[86] targets adults aged 40 to 74 who are invited to a risk assessment appointment. During the health check appointment a patient's blood pressure, blood cholesterol, smoking status, BMI and physical activity status are used to assess CVD risk. Recent NICE guidance advocates simultaneously assessing T2D risk with a risk score and a blood test alongside an NHS Health Check.[9] Individuals at high risk may then be referred for further health care, including preventive lifestyle interventions.

## 3.8 Summary

The high prevalence of T2D together with knowledge of aetiology, risk-factors, inequalities and sub-clinical conditions provide the background for T2D prevention research and underlines the importance of T2D prevention for public health. In the next chapter, I review the extensive evidence base for T2D prevention and select studies that provide evidence to support different evolutionary stages of intervention development and evaluation: from early feasibility studies, via efficacy and effectiveness evaluation, to implementation.

# CHAPTER FOUR: TYPE 2 DIABETES PREVENTION RESEARCH IN NEWCASTLE: A REFLECTION

The foundation for diabetes prevention work at Newcastle University was in train when I joined and interventions for T2D prevention in Newcastle have developed in parallel with preventive initiatives elsewhere. I have been privileged to have had excellent opportunities and considerable autonomy to contribute to and drive forward this valuable work. Along the way I have developed research skills, refined and expanded my collaboration and communication skills and worked through practical problems and solutions. The experience and insight gained from working in diabetes prevention over a number of years has provided the foundation for my thesis and this chapter tells the story of my work, from my own perspective. By relating this story chronologically, I have shown how my thoughts and ideas have developed. This history also provides the context for the published papers included in this thesis.

## 4.1 Background

The Newcastle Heart Project (NHP),[87] which was a cross-sectional study of risk factors for cardiovascular disease and T2D in different ethnic groups in the North East of England, provided the epidemiological basis for subsequent preventive research. This study demonstrated differential risk of T2D and cardiovascular disease for different ethnic groups and thus raised issues regarding equity for design of preventive interventions. The Newcastle IGT study tested the feasibility of lifestyle intervention, where participants were white European adults with IGT.[88] This study had improved glycaemic control as a primary outcome and acted as a pilot for EDIPS locally. The intervention delivery strategy, eventually used in the Newcastle arm of EDIPS derived from the Newcastle IGT study. EDIPS Newcastle, built on the Newcastle IGT study, with T2D incidence as a primary outcome.[89] The EDIPS collaboration was co-ordinated from Helsinki in Finland. The studies in this collaboration had a common protocol to facilitate data collation. There were also common intervention goals, but some flexibility in intervention delivery.

## 4.2 European Diabetes Prevention Study

When I joined Newcastle University as a Junior Research Associate, the EDIPS-Newcastle RCT was part way through recruiting participants. To complete the recruitment I engaged local primary care practices where practitioners identified adults likely to be at risk of future T2D by searching their practice databases for

patients with risk factors, including hypertension (Blood pressure 160/90 mmHg), overweight or obesity (BMI ≥ 25 $kgm^{-2}$), and family history of T2D. I then worked with the practice to invite people with risk factors to come to the Royal Victoria Infirmary in Newcastle for assessment. The assessment included an OGTT and those who were identified with IGT on this first screening were invited for a second OGTT to determine persistent IGT. People diagnosed with T2D were excluded from the study and their primary care physician was informed.

The primary outcome of the EDIPS-Newcastle intervention was T2D incidence. The risk reduction in the intervention group compared with the control group was 55%, (RR 0.45, 95% CI 0.2 to 1.2), which was similar to the 58% risk reduction (HR 0.4, 95% CI 0.3 to 0.7; p<0.001) demonstrated in the Finnish DPS. Analyses of EDIPS-Newcastle primary and secondary outcomes were published in my first submitted paper.[11]

**SP1. Prevention of type 2 diabetes in adults with impaired glucose tolerance: the European Diabetes Prevention RCT in Newcastle upon Tyne, UK** *Penn L, White M, Oldroyd J, Walker M, Alberti KGMM, Mathers JC*: BMC Public Health 2009; 9(1): 342

The flow-chart in this paper outlines the recruitment procedure, which indicates that identification of persistent IGT was time consuming and burdensome. The flow-chart should make this difficulty clear, but actually doing the assessment work has greater personal impact and I appreciated the problems of persistent IGT as a recruitment criterion (e.g. number needed to test, variability of IGT between sequential tests). By the time the EDIPS-Newcastle results were ready for publication both the DPS and DPP had already published their outcomes. [12, 90] Therefore we knew that additional analyses would improve the paper and its publication potential. Whilst working on the EDIPS-Newcastle I completed a qualitative study associated with the Newcastle-EDIPS, relating to participants' perspectives on maintaining behaviour change, which was subsequently published (not included here as this publication resulted from previously examined work).[18] Partly through this qualitative work I developed an additional analysis plan for secondary outcomes from the EDIPS-Newcastle. The underpinning behaviour change theory for EDIPS-Newcastle was the Transtheoretical Model. Motivational interviewing techniques were of key importance to the individualised intervention delivery strategy. Sometimes I sat-in on the consultations when the dietician and / or physiotherapist who delivered the intervention were counselling

participants. A tenet of motivational interviewing is about enabling people to plan their own individual actions and set goals for themselves. Through listening to the dietician I appreciated that there was clearly a conflict between motivational interviewing techniques and externally set goals (e.g. for weight loss targets of 5% as advised in the EDIPS-protocol). I also appreciated that maintenance of lifestyle change was a particularly important feature of this prolonged intervention. These ideas helped to formulate additional analysis for the first EDIPS-Newcastle paper. I designed and conducted an explanatory analysis of EDIPS-Newcastle data to assess beneficial change of any magnitude, which was maintained for two or more years, in the secondary outcome measures (weight loss, increased physical activity, reduced percentage dietary fat intake, increased percentage carbohydrate intake, and increased dietary fibre intake). This 'direction of change' analysis within the EDIPS-Newcastle data was designed to assess whether small beneficial changes that were maintained would be important for T2D prevention. The analysis suggested that this was likely, but the small sample size of the Newcastle data-set alone was a limitation for conclusive analyses.

In conducting the EDIPS-Newcastle trial I began to question the use of 2hrPG for assessment of an individual's ability to cope with a glucose challenge, which is the rationale for determining IGT. During the assessments I collected blood samples at baseline, 30, 60 and 120 minutes after ingestion of an OGTT load. I processed these samples during the same morning. There had been some research on the shape of the OGTT curve that provided evidence to support my hypothesis that the one hour plasma glucose would be a better proxy than 2hrPG for estimating the area under the OGTT curve. My interest in one hour glucose provided impetus for my pro-active effort in the collation of the full EDIPS data set. On its own the EDIPS-Newcastle dataset was too small for meaningful secondary data analysis. Collation of the EDIPS data was planned from the start of the EDIPS-Newcastle study, but as the DPS results were already published, and as the EDIPS collaboration was less extensive than was originally envisaged, the will to complete the data collation could have foundered.

I prepared a synopsis, based on various biomarkers for prediction of T2D with a preliminary analysis using the EDIPS-Newcastle data-set to demonstrate the potential for this exploratory analysis in the collated data and sent it to the EDIPS co-ordinating team in Finland. We were able to discuss this and other analyses that might be

possible with collated EDIPS data during the 5th World Conference for Prevention of Diabetes in Helsinki in 2008. Nevertheless it took a long time and much effort for the data from Finland, The Netherlands and our own work from the UK to be collated, checked and distributed to each of the three collaborating centres. We agreed the method for this in principle during a meeting in Helsinki in November 2008. During this meeting we also allotted leadership for various possible secondary analyses (brief outlines). To facilitate collation of the EDIPS data I prepared the common data template as an SPSS file and supplied the EDIPS-Newcastle data. The data from Maastricht were supplied using my template by Annemieke den Boer, the work of putting the three EDIPS files together was mostly done by Jaana Lindström in Helsinki, and the three of us checked the data.

After the EDIPS data had been collated, checked and distributed I was offered the opportunity to draft a paper reporting the analysis of the EDIPS primary outcome: effect of lifestyle intervention on incidence of T2D, thus giving Newcastle the lead on this paper. By this time a number of RCTs had already been published demonstrating the preventive effect of lifestyle intervention and there was also review level evidence. The EDIPS primary outcome was therefore not novel. However, I was appointed to serve as a professional member of the NICE Programme Development Group (PDG) for NICE guidance on 'Prevention of type 2 diabetes: risk identification and intervention for individuals at high-risk.' I used information and ideas gained through this experience to formulate additional analyses for the EDIPS paper. (SP2) Essentially the explanatory analysis in this paper is about how efficacy research might be revisited to evaluate evidence based guidance. Working with the NICE guidance team as a member of the PDG was an intense experience. Even though the evidence base for T2D prevention is extensive, research evidence is not guidance. The focus on producing 'evidence based' guidance from the available evidence was salutary. It was also illuminating to hear how group members reflected their own perspectives within the group, which could lead to controversy and engendered very thoughtful discussion. The details of NICE PDG discussions are confidential within the group, but I believe I made a valuable and influential contribution.

The first analysis of the collated EDIPS data is the subject of my second submitted paper.

**SP2. Weight loss in prevention of type 2 diabetes in adults with impaired glucose tolerance: the European Diabetes Prevention Study RCT**, L Penn, M White, J Lindstrom, A den Boer, E Blaak, J G. Eriksson, E Feskens, P Ilanne-Parikka, S M Keinänen-Kiukaanniemi, M Walker, J C Mathers, M Uusitupa, J Tuomilehto. *PLoS ONE 2013;**8**(2)*

Analysis of the EDIPS primary outcome, T2D incidence, makes a contribution to the evidence for diabetes prevention and extends this to three European populations. I sought to add value to this publication by including an analysis based on achievement and maintenance of the 5% weight loss goal advocated in the EDIPS protocol and in NICE guidance. In planning this explanatory analysis I was aware that it would inform further development of translational diabetes prevention studies. I also designed and conducted analyses of T2D incidence in EDIPS sub-sets defined by baseline blood parameter ranges for FPG and HbA1c. These hyperglycaemia measures are more convenient than IGT for risk assessment and thus might be considered more suitable as inclusion criteria for translational studies. The NICE guidance advocated a risk score assessment followed by a blood test (FPG or HbA1c) with specific cut-points to identify individuals at high-risk for the application of preventive intervention, but the evidence for effective prevention of T2D is from populations where high-risk is defined by IGT. I maintain that this extrapolation of evidence beyond the population where the evidence was generated is a significant weakness in the NICE guidance.

Although the EDIPS interventions were successful in demonstrating the efficacy of lifestyle interventions in reducing T2D incidence there were some individual participants, in both the intervention and control groups, who were diagnosed with T2D very early in the trials. As the changes advocated in the intervention involved diet and physical activity modifications it is possible that these may have taken some time to implement. Also, although the EDIPS intervention was intensive, in terms of number of contact occasions, the beneficial lifestyle changes advocated were quite modest. Consequently I began to consider whether a variation in these targets, such as for more extreme and immediate lifestyle change, might be more appropriate for people at imminent risk of T2D, ( i.e. those highly likely to develop T2D within one or two years).

Recent work has shown that, at least in the early stages, T2D can be reversed by extreme dietary restriction.[58] There may therefore be a value in distinguishing different risk groups within the progression of hyperglycaemia, for example differentiating those with a T2D risk probability of 50% ten years from those with a T2D risk probability of 50% in two years.

The most pressing need and greatest contribution for health improvement in the population at risk is for the effective and sustainable translation of interventions for prevention of T2D to real world settings. However, this should not preclude the continuing quest for greater scientific understanding of the underlying mechanisms and aetiology (through epidemiology, biochemistry, physiology or systems biology), of progression to T2D. This knowledge will continually progress theory based possibilities for intervention improvement.

An interest in the potential to identify those people at imminent risk of T2D and the potential utility of the one hour plasma glucose parameter led to an analysis of bio-marker predictors in the collated EDIPS data set, which is being prepared for publication.

## 4.3 European Nutrigenomics Organisation

Following completion of the EDIPS-Newcastle trial I took the opportunity to work with the Newcastle Work-Package (WP6 Human Studies) of the European Nutrigenomics Organisation (NuGO). The work encompassed by NuGO was mostly lab-based, but the human studies work package included study design and ethics where I contributed to discussions. This was an interesting and productive learning experience that broadened my knowledge and linked my current work to my original interest in physiology and biochemistry, which was the subject area of my BSc. Within weeks of starting this work I had collected pages of new vocabulary around 'omics' techniques all of which makes reading papers relevant to my current work that include this terminology more accessible. During the NuGO programme I helped to organise a workshop on 'Design of human nutrigenomics studies' and two workshops on assessment of dietary intake. I have included a published report from one of these, where I was first author, as supporting documentation.[91]

Of particular immediate interest for assessment of dietary intake in translational studies is the potential to use Multiple Source Methods (use of 24 hour recall together with population level food frequency questionnaires). Through the EDIPS-Newcastle work I was very aware of the respondent burden imposed by the completion of three day food diaries, which was the dietary data collection method in this protocol. Not only did we have missing data, where people had failed to complete food diaries at all, but the quality with which these were completed was variable and in many cases the completion quality 'tailed off' markedly after the first day. Dietary assessment is notoriously difficult and the respondent burden is a particularly important consideration for translational studies and applying an intervention to people with low literacy or where there are language issues.

An objective measure of dietary intake, as has been evaluated in small scale metabolomics studies, would be useful. From the information provided to the workshop I thought the possibility that urine pH (acidity) might be used to assess intake of fruit and vegetables had interesting possibilities. This measure has been used in population cohort studies, but had not been used to assess change in intervention studies. My suggestion (to use urine pH to assess change in dietary intake of fruit and vegetables) has subsequently been included in an on-going project at Newcastle assessing the relationship between blood pressure and intake of fruit and vegetables (VegBP), which is currently underway. Depending on the outcomes there could be potential to progress this.

**SD1. Assessment of dietary intake: NuGO symposium report.** *Linda Penn, Heiner Boeing, Carol J. Boushey, Lars Ove Dragsted, Jim Kaput, Augustin Scalbert, Ailsa A. Welch and John C. Mathers***,** Genes & Nutrition, 2010. 5(3): p. 205-213.

## 4.4 The 'New life New you' translational intervention

In 2008 an opportunity came about, through the 'legacy' requirement associated with the London 2012 Olympic and Paralympic Games. Integral to the bid for the London Games was the aspiration that the Games would support and inspire more people in the UK to enjoy sport and physical activity. In the North East of England part of the local '2012 Nations and Regions Group' remit was to address local contributions to this aspiration and 'unlock sustainable regional benefits' including in the area of health and physical activity. An expert steering group, with representation from Sport England,

local government, the NHS, Diabetes UK and Newcastle University was convened to consider options. This group proposed an outline plan for the development and pilot evaluation of a community based intervention for prevention of T2D in adults at risk, with the potential to implement a pragmatic T2D prevention intervention across the North East region, with a particular focus on communities most in need. The outline proposal was for an intervention to be led by fitness trainers in local authority leisure and community settings in a North East area with high levels of socio-economic deprivation, where there was likely to be a high prevalence of adults at risk of future T2D. The cross-sector approach, bringing together health and leisure sectors in partnership, was in line with the contemporary national policy and regional strategy.

The outline structure of the intervention and the decision to inculcate robust evaluation procedures from the start of the intervention development was determined by the steering group. I then had the opportunity to work with the intervention delivery team to develop this intervention pilot and, as I had just completed the EDIPS-Newcastle trial, this was timely.

At the time I had just completed a systematic review for the BMJ Health Intelligence web site so I was able to use this evidence review in planning the intervention. Although this website no longer exists, I have included the text we supplied to the BMJ as supporting documentation.

**SD1. BMJ Intelligence: Public Health Evidence section: Prevention of type 2 diabetes**
*Penn L, White M. 2006 (Website no longer accessible)*

The systematic searches for identification of IGT that were provided by the BMJ team for this review did not include a risk score tool. However, after visiting Finland for a conference associated with the FIN-D2D translational study I appreciated the utility of risk scores. I learnt the difference between a prospective risk score for future T2D (that could therefore be used as a proxy to identify IGT), developed from cohort study data, and prevalence T2D risk score, developed from cross-sectional data. We secured agreement to include FINDRISC within the BMJ review. This important quality distinction between a risk score derived from cohort data and a cross-sectional score has been highlighted in a recent review paper [92] and risk scores compared in another recent paper.[71] This risk-score method for identification of individuals at high-risk was

vital for the development of the NLNY pilot where there was no provision for blood testing and using an OGTT would be impractical.

In developing the NLNY intervention the small fieldwork team had considerable autonomy within the outline structure. There were many challenges and compromises, but the desire to realise a workable intervention design with embedded evaluation, together with mutual respect for each other's professionalism and differing expertise allowed tensions to be resolved within this small team. I believe this model, which allowed collaborative operational optimisation of the intervention, offered an ideal solution and provides lessons for translational research more generally. Even when an intervention has been shown to be effective in one setting, the application to a different context requires thorough piloting.

Details of the translation process are provided in the chapter entitled 'Towards the translation of research evidence to service provision: experience from North East England, UK' in the book published for the World Conference for Prevention of Diabetes held in Dresden, Germany in 2010. I was invited to submit a chapter and I chose to report on both the EDIPS-Newcastle and the 'New life, New you' pilot study. I explained ways in which the evaluation procedures and requirements in the translational study were informed by and differed from the trial evaluation procedures. I have included this book chapter as a supporting document.

**SD2. Towards the translation of research evidence to service provision: experience from North East England, UK.** *Penn L, Lordon J, Lowry R, Mathers JC, Smith W, Walker M, White M.* in Diabetes Prevention in Practice, Peter Schwarz, Editor. 2010: Dresden.

Following the conference I was invited to revise this chapter for publication in a special edition of the British Journal of Diabetes and Vascular Disease focussing on prevention of T2D. At this time I was able to include results from the NLNY pilot study first cohort at six-months. The resulting publication is my fourth submitted paper.

**SP3. Translating research evidence to service provision for prevention of type 2 diabetes: development and early outcomes of the 'New life, New you' intervention.** *Penn L, Lordon J, Lowry R, Mathers J, Smith W, Walker M, White M.* **Br J Diabetes Vasc Dis** *2011;11:175-181*

Consideration of the translational process at a local level and an appreciation of differing evaluation requirements through different phases of intervention development set the seed for the wider consideration of this process, within diabetes prevention interventions, which is the overall theme of my thesis.

As a feasibility study NLNY cannot provide robust evidence of effectiveness. However it proved timely for the NICE Programme Development Group and the subsequent guidance for diabetes prevention. [93] The NLNY intervention is also of current interest because it has been designed as a health and sports (leisure service) partnership. Health promotion services have been transferred to Local Authorities as part of the reorganisation of the NHS and pPublic Health resulting from the Health and Social Care Act, 2012. [94] The NLNY outcomes at one year are the subject of my fourth submitted paper.[13]

**SP4. Feasibility, acceptability, and outcomes at 12 months follow-up of a novel community based intervention to prevent type 2 diabetes in adults at high risk: mixed methods pilot study.** *Penn L, Ryan V, White M.* **BMJ Open** *2013; **3**(11).*

In this study, 218 participants were recruited to the intensive lifestyle programme. Follow-up at 12 months was completed by 134 (61%) participants. Estimated mean (95% CI) changes from baseline were: weight -5.7 (-7.8 to -2.8); -2.8 (-3.8 to -1.9)kg, waist circumference -7.2 (-9.2 to -5.2); -6.0 (-7.1 to -5.0) cm, and PA level 7.9 (5.8 to 10.1); 6.7 (5.2 to 8.2) MET-hours per day equivalent, for men and women respectively (from covariance pattern mixed models). Participants' reported an enjoyable, sociable, and supportive intervention experience. The high retention and positive outcomes at 12 months follow-up, were encouraging indicators of acceptability and likely effectiveness.

The qualitative study associated with the EDIPS-Newcastle trial provided evidence to underpin the development of the NLNY study and is cited in the NICE-R4.[9] Before NLNY started the project team commissioned social-marketing consultations with key stakeholders; both prospective staff and participants. The social marketing reports identified participant preference for single sex activity sessions and the importance of seamless access to the intervention. When the first NLNY cohort had completed one year in the study, I was able to plan some more formal in-depth qualitative research.

The topic guide for this built on the work I had done for the EDIPS-Newcastle qualitative study and also took advantage of more recent work relating to behaviour change strategies. Following discussion with co-authors, I used the refined Theoretical Domains Framework for behaviour change to categorise themes emerging from the qualitative data.[95, 96] In the early stages of intervention design we actively planned to use the social potential of physical activity sessions to promote engagement with the intervention. The qualitative analysis, together with experience from the feasibility study, has contributed to intervention refinement. The importance of social factors in promoting intervention recruitment and retention, and social support for maintaining behaviour change post intervention were important findings from this qualitative research. The publication resulting from this qualitative evaluation is my fifth submitted paper. [17]

**SP6. Participants' perspectives on making and maintaining behavioural changes in a lifestyle intervention for type 2 diabetes prevention: a qualitative study using the theory domain framework.** *Penn L, Dombrowski SU, Sniehotta FF, White M*. **BMJ Open** 2013;**3** (6)

This qualitative evaluation contributed to the acceptability assessment of the NLNY intervention and highlighted intervention features that promoted recruitment, retention in the intervention and maintenance of behaviour change after the follow-up. Social influences, and intentions and goals were dominant themes in all phases of behaviour change. The environmental context and resources were reported as important for the intervention participants, as was anticipated for this community from an area of social deprivation.

## 4.5 Impact of organisational changes

Following the NLNY feasibility study there was a period of funding insecurity. The trainers were unable to guarantee a full intervention programme to new recruits. There were also difficulties because some 'original' participants, recruited early in the programme failed to move on to more independent physical activity and were still accessing NLNY sessions. In response the trainers deviated from the original protocol, which was that all new recruits would receive a 10 week programme, and began integrating new recruits into existing sessions. The consequence was fewer new recruits and continuing difficulties where people failed to exit the programme.

Although entirely unplanned this has proved very useful for the future in underlining the need for clear fidelity monitoring and explicit guidance.

### 4.6 New Life New you service level agreement

Following the NLNY pilot study and the period of funding insecurity, I worked closely with both the local NHS commissioning team and the trainers to develop a written contractual 'Service Level Agreement' (SLA) for the commissioning of the NLNY intervention as a service provision in the local area where it was piloted. I used the analyses from the first two cohorts of the pilot study to supply realistic 'Key Performance Indicators' (KPIs) that have been included in the SLA. Additional KPIs will be incorporated as further data become available. I also wrote a detailed intervention manual that includes the relevant NICE guidance.

The fact that some people tended to stay involved with the NLNY programme even when their year was complete was inconvenient for the smooth running of recruitment and progression, but it was also testament to the quality of the intervention delivery. The qualitative work helped in understanding and promoting the potential of a peer-support role for participants who, having completed the NLNY intervention might be able to volunteer their time and commitment to helping new recruits who had recently completed their 10 week programme. Requirements relating to the enrolment and training of community members are included in the SLA. We have identified possible roles for community member as 'awareness champions,' to promote recruitment to the programme and as 'peer-supporters' to encourage continued engagement with the programme.

The administration of the NLNY intervention, to ensure accurate and relevant data collection, was a challenge for the fitness trainers in the early days. I worked with our database designer to plan the first database. This database has now been revised to automatically generate the KPI service monitoring reports that are required as part of the SLA. I have also prepared web-access forms for additional data input. This dual input approach both simplifies the database and provides an accuracy check.

The DPP based studies (e.g. the DEPLOY study) access a protocol with detailed session plans.[97, 98] This 'top down' detailed approach might be appropriate when intervention adherence is considered the most important intervention feature, and it may have

utility where the delivery staffs are minimally trained. However the NLNY fitness trainers were experienced professionals and from the start of intervention development they rejected this degree of prescription, citing their previous experience with similarly prescriptive weight management programmes. Also the NLNY intervention, which relied on a novel 'do and reflect' model, would not accommodate this degree of session detail. The activities provided needed to be resource compatible and responsive to participant preferences. The development of KPIs as part of the SLA allowed flexibility in delivery and will be evaluated in the next phase of the local service implementation.

## 4.7 Adaptation of the New life, New you intervention for ethnic minority groups

The NLNY intervention has been extended and adapted to be more engaging and appropriate for individuals at high-risk within local ethnic minority communities. The intervention delivery for women is being conducted by a community provider where the lead fitness instructor is from the local South Asian (SA) ethnic community. This model for intervention provision is described as a 'Community Interest' model, which is a not-for-profit business model. As a result of the rapid recruitment of women to this adaptation of the NLNY intervention the community provider has recruited other women from the local ethnic community as trainers. The local NHS health improvement service has provided funding support so that these SA women can receive basic training, through a Register of Exercise Professionals (REPS) accredited provider, as health and fitness trainers, to allow them to deliver the NLNY intervention. These newly qualified trainers then work with a more experienced trainer. This co-working is an important continuation of their training that ensures the quality and supportive ethos of the programme is maintained. These trainers work on a casual, session by session basis and are therefore paid solely for the hours they work. This community interest model therefore epitomises a vision for the way peer supporters might become incorporated. The NLNY adapted provision for men from the local ethnic minority community has been slower to progress.

I took advantage of the rapid and successful expansion of the ethnic adaptation of the NLNY programme to conduct qualitative interview studies with the SA women participants and the newly qualified trainers. This was an excellent opportunity for some interesting work that will help to elicit participant perspectives and further

consider the potential of this intervention delivery model. We also plan to evaluate the feasibility, acceptability and outcomes at 6 and 12 months follow-up of the adapted intervention.

A necessary part of this NLNY adaptation for the local ethnic community is a widening of the age range for recruitment, in line with recent NICE guidance for communities at risk. As the NICE guidance applies to risk factor assessment in people of all ethnicities, this extension in age will be similarly applicable to the whole NLNY recruitment cohort. The intervention design which allows for grouping of 'like-minded' participants facilitates the grouping by age, ethnicity, and /or sex as required by the participants and as considered appropriate by the intervention providers.

## 4.8 Current and future plans

The recruitment and retention success of the NLNY model has resulted in pressure, from maternity services, to incorporate provision for women who have had gestational diabetes. Interestingly the original Wien study was conducted in women with previous gestational diabetes and with current IGT, thus efficacy of preventive intervention is this high-risk group has been tested.[99] Recent qualitative work by Lie et al[100] has explored the feasibility of preventive intervention for this population and uncovered important contextual factors. Current plans for the NLNY local provision are to include gestational diabetes as a single risk criterion for recruitment and this variation in recruitment will be evaluated separately. Design of a specifically tailored adaptation of NLNY is a future option.

## 4.9 Summary

Review and analysis of the guidance literature and review and analysis of the T2D prevention literature are no substitute for day to day experience of working to progress intervention development and evaluation in the field, but these three strands of knowledge are complementary.[101] In relation to my research question the most novel contribution of my empirical work is regarding the implementation stage of the evolutionary progression in intervention development. The implementation stage is where the literature is most scarce and where context becomes increasingly relevant. The options for service provision are necessarily different in different health care and public health contexts. An implementation strategy that works in one country is not

necessarily transferable to another, although lessons can be learnt from different experiences.[102]

My research publications in support of my thesis are included in appendices A to E starting on page 95 and it may be appropriate to read these papers at this point. In the next chapter I review the wider literature relating to T2D prevention.

# CHAPTER FIVE: LITERATURE REVIEW AND SELECTION OF TYPE 2 DIABETES PREVENTION CASE STUDIES

## 5.1 Sources of evidence

This literature review is restricted to lifestyle interventions for individuals at high risk of future T2D, since that has been the focus of my work. It is not a standard systematic review. Extensive systematic reviews of T2D prevention literature have been completed recently,[9] It would not be appropriate to repeat these. Instead I have used a purposive approach to identify T2D prevention studies for high-risk individuals that provide evidence spanning different evolutionary stages in intervention development and evaluation. For my literature review I have drawn on:

- Four recent NICE systematic reviews:[9]
- A previous T2D prevention literature review that I co-authored for the British Medical Journal, 'Public Health Intelligence' web site (which is unfortunately no longer available online),[89]
- The Diabetes in Europe – Prevention using Lifestyle, Physical Activity and Nutritional intervention (DE-PLAN) final report, and publications, including chapters from the book produced for the World Conference for Prevention of type 2 diabetes in 2010.[103-105]

### *5.1.1 NICE reviews*

The NICE public health guidance for T2D prevention was split into two: the first guidance for 'Population and community interventions,' was published in May 2011,[80] and the second for, 'Risk identification and interventions for individuals at high risk,' was published in July 2012.[9] The second guidance is most relevant to my thesis.

To inform the second guidance, NICE commissioned four systematic literature reviews, all of which were conducted by the University of Sheffield, Public Health Collaborating Centre at the School for Health and Related Research (ScHARR).[9] The first of these (NICE-R1) was 'Identification and Risk Assessment of adults with pre-diabetes,' the second (NICE-R2) was a 'Systematic review and meta-analysis of lifestyle, pharmacological and surgical interventions' and is restricted to RCT evidence, the third (NICE-R3) was of, 'Mechanisms of successful interventions and translation of major

trial evidence to practice,' and the fourth (NICE-R4) reviewed ' Barriers and facilitators affecting the implementation and effectiveness of interventions to assess the risk of progression to diabetes, and the implementation of preventive interventions and behaviour change'.

*Strengths:* The NICE reviews were systematic, comprehensive within the scope of the guidance, good quality and up to date (guidance published July 2012, reviews from 2011). Included studies were quality assessed using Jadad[106] scores and NICE checklist scoring system.[9]

*Limitations*: During the process of guideline development the title of the NICE guidance was changed. However, the reviews reflected the original title which was: Preventing the progression of pre-diabetes to type 2 diabetes in adults. This focus on pre-diabetes was a limitation, both for the conduct of all the reviews and for the development of the NICE guidance. Effectively by limiting high-risk to 'pre-diabetes', NICE had pre-judged the most appropriate risk assessment procedure that is pertinent for translational interventions and thus excluded a body of relevant evidence.[107]

Jadad scoring for quality assessment relies on features of randomisation.[108] One of the three Jadad questions: 'Was the study double blind?' is not appropriate for lifestyle intervention studies, which limits the contextual utility of this quality assessment.

### *5.1.2 BMJ Health intelligence*

Our review for BMJ Health Intelligence (2008) included four sections: 1a on interventions that aim to prevent or delay the onset of T2D in adults with IGT, 1b cost considerations for 1a, 2a identifying adults with IGT, and 2b cost considerations for 2a. (The web-site text is submitted as supporting documentation SD1 in Appendix A. This web-site is no longer accessible)

*Strengths:* The searches were conducted systematically by the BMJ team who supplied a list of papers to review. For each study we prepared a short 'fact file' with the title and answers to the questions: What is it? Does it work? How does it work? Does it only work in certain groups of people? This unusual 'fact file' format was specifically requested by the BMJ team to answer key assessment questions. This review also included papers that reported secondary analyses associated with the main prevention trials.[109-111]

*Limitations:* Intervention studies were restricted to review level and RCT evidence in adults with IGT and the time span of search was limited to 2000 -2007.

### *5.1.3 DE-PLAN report and publications*

Following the completion of the Finnish DPS, a large multicentre European project: Diabetes Prevention in Europe (DE-PLAN)[107] was introduced and funded by the European Commission public health 5th Framework. The objectives for the DE-PLAN project were to: 'assess the T2D risk in European populations and implement and evaluate a lifestyle intervention programme to prevent T2D in high-risk individuals.'[72] The DE-PLAN project involved diabetes prevention interventions conducted in 17 European countries (21 partner centres and 4 collaborating centres) between 2005 and 2008 (Figure 9). These studies were not included in the NICE translational studies review as they did not recruit participants with 'pre-diabetes'.

*Strengths:* The DE-PLAN programme aimed to address the development of national community-based T2D prevention programmes systematically throughout European countries.

*Limitations:* Most of the DE-PLAN studies were conducted with a relatively weak before-and after study design and there are few publications to my knowledge (to date) in peer-reviewed journals.

## 5.2 Study selection criteria

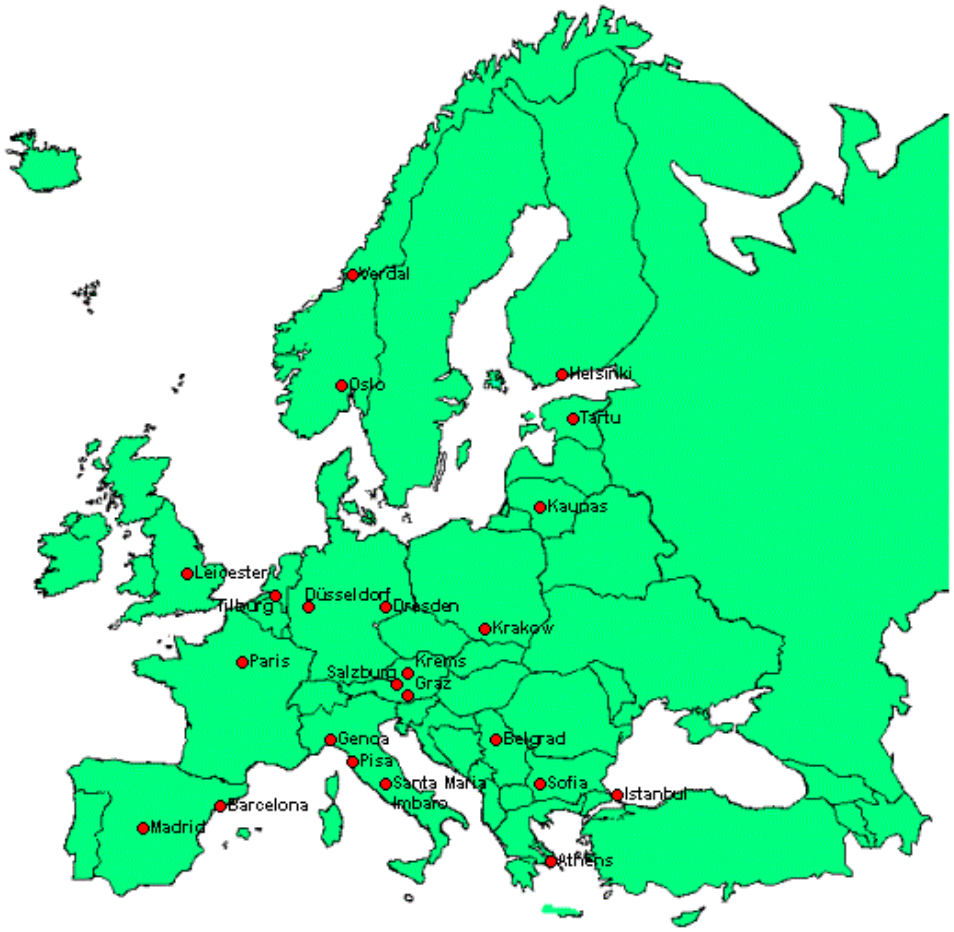
The term 'evolution' Nutbeam 1999 (page 41) or 'evolutionary' Ogilvie et al (2011), to describe the progression in development and evaluation of complex interventions is useful to clarify an assumption that each stage should add evidence that will inform the next stage.

In reviewing the literature, I have selected studies for analysis using the criterion:

> Does this study provide evidence to support evolutionary, staged progression in development of interventions for T2D prevention?

I have narrowed the selection around the relevance to UK service provision, since this is the context for my work.

**Figure 10: DE-PLAN map showing the centres that participated in the DE-PLAN programme**




## 5.3 Included and excluded studies

### *5.3.1 Feasibility and efficacy studies*

An earlier systematic review of RCT evidence conducted by Gillies et al in 2007,[6] was updated in NICE-R2. The Gillies review included 21 primary studies of which 17 were included in a meta-analysis and, of these, 9 were lifestyle interventions. Meta-analysis showed a pooled hazard ratio of 0·51 (95% CI 0·44 to 0·60) and numbers needed to treat to prevent one case of T2D were 6.4 (95% CI 5.0 to 8.4).[6] NICE-R2 included 14 T2D prevention lifestyle intervention studies: eight that were included in the Gilles review, four new studies (including my submitted paper SP1); and three longer-term follow-ups of studies included in the Gilles review. Our BMJ evidence review included papers reporting lifestyle components in secondary analyses of the DPS RCT data, which might inform intervention development.[109, 111, 112 113]

*Included studies:* The first large diabetes prevention RCTs with individual randomisation were the Finnish Diabetes Prevention Study (DPS)[12] (published in 2001), and the US Diabetes Prevention Programme (DPP)[114], (published in 2002). The DPS recruited 522 overweight adults with IGT and randomised to lifestyle (diet and exercise) intervention or usual care control. The DPP recruited 3234 adults with IFG and IGT and randomised to three groups: lifestyle (diet and exercise), metformin, and placebo control group. Papers reporting secondary analyses of the DPS and DPP data have evaluated: diet, insulin sensitivity and achievement of lifestyle targets.[109, 111, 115, 116] In addition there were longer-term follow-up studies of the DPP and DPS.[113, 117, 118] I have selected the DPS and DPP RCTs for further analysis because these two efficacy trials are antecedents to several translational studies as identified in NICE-R3[9].

The DPS has particular relevance to my submitted papers. When the DPS was planned there was an intention to conduct similar, but smaller sized, intervention studies in 10 other European centres outside Finland: the European Diabetes Prevention Study (EDIPS). The EDIPS centre in Maastricht, The Netherlands (SLIM study) and our centre in Newcastle upon Tyne, UK (EDIPS-Newcastle) completed their study arms. Interventions were based on the DPS protocol, although there was some flexibility for local variation in intervention delivery. These two studies were included in the NICE reviews and they have associated translational studies. The Newcastle-IGT RCT, [88, 119]which was not identified by the NICE-R2 because the primary outcome was change in glycaemia rather than T2D incidence, served as a methodological pilot for EDIPS-Newcastle.

*Excluded studies:* Other large T2D prevention RCT have been conducted in Japan[120], India[121], and Sweden.[122] Although these contributed to answering the efficacy question they do not fulfil my selection criterion for analysis because they were not associated with translational studies. Also they are less contextually relevant to the UK.

The NICE-R2 identified two early lifestyle intervention studies with T2D incidence as an outcome: the Whitehall Borderline Diabetes Study (1979),[123] and the Wein study (1999).[99] These early studies have design and sample size limitations, but provided evidence of feasibility that contributed to the DPS and DPP. They were not specifically designed as feasibility studies.

### *5.3.2 Real world effectiveness studies*

One of the review questions in NICE-R3 was about translation of RCT evidence to 'real world' situations. The review methods and study selection criteria were detailed in the report.[9] All the translational studies identified were described as either DPP or DPS based (meaning the study design was influenced by the DPP or DPS protocols). Most used a relatively weak before-and-after study design. Of 789 papers retrieved from the searches 13 papers were included in the translational study section of the NICE-R3. Nine intervention studies (10 papers)[97, 124-131] were based on the DPP protocol and conducted in the US, whilst three were based on the DPS protocol, two in Finland[132, 133] and one in Australia. [134]

NICE also commissioned 'A pragmatic review of risk identification and interventions to prevent type 2 diabetes in high risk adults in disadvantaged and vulnerable groups'.[93] This review was restricted to UK based projects that targeted adults at high-risk of developing T2D with a focus on vulnerable groups. Two studies that assessed intermediate health outcomes were included.[93]

The DE-PLAN project involved 25 centres (21 partners and four collaborators) in 17 European countries. At the time of the final report risk assessment data collection was completed for 15, with a further seven expected and 21 of the centres reported participation in intervention activities (small pilot studies in three of these). No intervention outcomes were included in the report, but there have been a few subsequent publications from individual countries.[135-137]

*Included studies:* I have included all three DPS based translational studies: the FIN-D2D study[133], which was associated with the Finnish National Diabetes Prevention Programme;[138] the GOAL study, also from Finland; and the GGT study, from Australia, that was adapted from the GOAL study. All these illustrate an evolutionary stage in intervention development that can be traced through a line of succession. The DPP based translational studies are less relevant to my work as there is no direct succession. Two of the DPP based studies were delivered in community settings and I have included one of these: the Diabetes Education & Prevention with a Lifestyle Intervention Offered at the YMCA (DEPLOY) study as an example of a DPP based translation.[97] Our 'New life, New you' (NLNY) project in Middlesbrough[15] was one of

the two interventions identified through the NICE commissioned pragmatic review that assessed intermediate health outcomes.[9]

Recently, the outcomes of Catalonian PREDICE study, which was part of the DE-PLAN programme, have been published.[102] Unusually, within this DE-PLAN programme the PREDICE study included a control condition (non-randomised) comparator and T2D incidence was the primary outcome. PREDICE was therefore an important translational study, providing more robust evidence than those studies with weaker study design and with weight loss as the primary outcome. The DE-PLAN study in Dresden was part of the Saxon DPP programme which is included in the implementation section.[139]

*Excluded studies:* DPP based translational studies that were not delivered in community settings,[124, 125, 127-131, 140] and one DPP based that was delivered in a community setting, but was quite small and delivered in a rural African-American church setting which was less relevant to my research question. [126] The other intervention, with health outcomes (apart from NLNY), identified through the NICE commissioned pragmatic review was 'Khush Dil'. This study targeted South Asian adults living in Edinburgh.[141] The PODOSA trial, which was based on the DPS, has subsequently been developed and Khush Dil provided evidence for PODOSA.[142]

### *5.3.4 Implementation evaluations*

The distinction between effectiveness studies and implementation evaluation is sometimes unclear. In evolutionary progression an effectiveness evaluation should precede wider service provision and would generally be more localised and small scale. Service evaluation would then ideally take place once an intervention had become embedded.

*Included studies:* The FIN-D2D[133, 143] study was large scale and was conducted alongside the Finnish national diabetes care and prevention programme (DEKHO).[144] The Finnish national programme involved both population and high risk group approaches to diabetes prevention. The high-risk approach was delivered in primary care in five hospital districts.[104] The FIN-D2D implementation has a population level evaluation study in which those areas where the high-risk FIN-D2D intervention was provided were compared with other areas of Finland.[145] I believe this evaluation is

currently the only example of a population level follow-up to the implementation of T2D prevention and is important to the concept of evolutionary progression in demonstrating the potential for beneficial population level impact as the overarching outcome for public health interventions, as explained in the 'broader focus' expanded by Ogilvie et al (2009 and 2011)

One of the DPS based translational studies, the Greater Green Triangle (GGT) study in Australia was subsequently expanded to a service provision programme called 'Life!'[104] [146] This implementation outwith Europe, but derived from the DPS and the GOAL study, exemplifies an evolutionary route that included intercontinental researcher collaboration. Another large scale implementation programme, the Saxony diabetes prevention programme (Saxon-DPP) in Germany, recruited participants using a modified version of FINDRISC (in common with the DE-PLAN studies), but utilised the DPP intervention protocol.[147] [148] This exemplifies an evolutionary trail that draws from two antecedent RCTs. Both the Saxon-DPP and Life! programmes were delivered in community settings and therefore provide context relevant to NLNY.

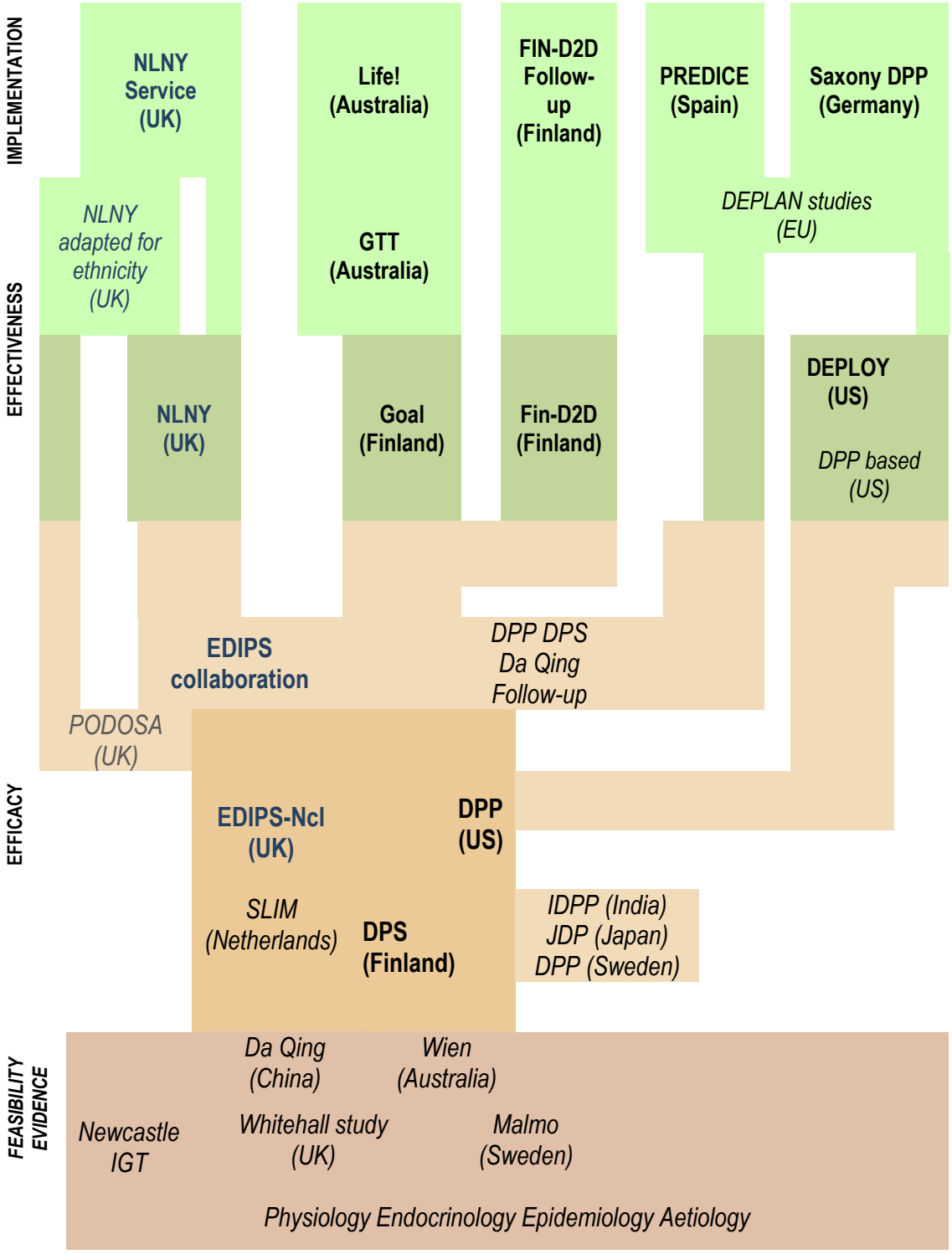
*Excluded studies*: To the best of my knowledge there are no other implementation evaluation studies linked to the DPP or DPS.

## 5.4 Summary

The studies that I have selected to illustrate the evolutionary stages in development and evaluation of interventions for T2D prevention are depicted in an evolutionary 'tree' of T2D prevention (Figure 10). I have used the visual metaphor of an evolutionary tree to show the evaluation stage (efficacy, effectiveness, and implementation) of included studies and to clarify their evolutionary lineage. In the next chapter I discuss my findings by drawing together my empirical work, the literature for primary prevention of T2D and published guidance for the development and evaluation of complex interventions to improve health.

**Figure 11: Interventions for prevention of type 2 diabetes as an evolutionary tree**

Studies selected from the literature to illustrate the evolutionary progression in type 2 diabetes preventive interventions and provide context for my submitted papers (Key and references below). A tree metaphor is used here to illustrate progression from wide roots via a common lineage (efficacy) with divergence and proliferation to multiple adaptations in real world settings with different social and environmental contexts.




**Bold black = studies selected from the literature for analysis**; *italics black = studies providing additional context*

**Bold blue = my submitted papers;** *italics blue = on-going work at Newcastle*

***Key to Figure 10*:** Interventions for prevention of type 2 diabetes evolutionary 'tree'

| | |
|---|---|
| **Life!** | Janus E, Best J, Davis-Lameloise N, et al. **Scaling-up from an implementation trial to state-wide coverage: results from the preliminary Melbourne Diabetes Prevention Study**. *Trials* 2012; **13**(1): 152. |
| **Life!** | Dunbar, J., et al. **Scaling up type 2 diabetes prevention programs: National and State interventions in Australia**, in Diabetes Prevention in Practice, P. Schwarz, et al., Editors. 2010, WCPD Dresden. p. 45 – 55 |
| **FIN-D2D Follow-up** | Salopuro T, et al. **Population-level effects of the national diabetes prevention programme (FIN-D2D) on the body weight, the waist circumference, and the prevalence of obesity.** BMC public health 2011;11(1):350. |
| **Saxony-DPP** | Schwarz, P.E.H., et al. **Development of a diabetes prevention management program for clinical practice**. Public Health Reports, 2007. 122(2): p. 258-63 |
| **GGT** | Laatikainen T, et al. **Prevention of type 2 diabetes by lifestyle intervention in an Australian primary health care setting: Greater Green Triangle (GGT) Diabetes Prevention Project**. BMC Public Health. 2007.19(7): p 249. |
| **PREDICE** | Costa B, et al**. Delaying progression to type 2 diabetes among high-risk Spanish individuals is feasible in real-life primary healthcare settings using intensive lifestyle intervention**. Diabetologia 2012; 55 (5):1319-28. |
| **NLNY 12 months** | |
| **NLNY 6 months** | Penn L, et al. **Translating research evidence to service provision for prevention of type 2 diabetes: development and early outcomes of the 'New life, New you' intervention**,. *British Journal of Diabetes and Vascular Disease* 2011; **11**(4): 175 - 81. |
| **GOAL** | Absetz P, et al. **Type 2 Diabetes Prevention in the Real World**. Diabetes Care. 2009; 32(8): 1418-20. |
| **FIN-D2D** | Saaristo T, et al**. Lifestyle intervention for prevention of type 2 diabetes in primary health care: one-year follow-up of the Finnish National Diabetes Prevention Program (FIN-D2D).** Diabetes Care. 2010; 33(10): 2146 |
| **DEPLOY** | Ackermann RT, et al. **Translating the Diabetes Prevention Program into the Community: The DEPLOY Pilot Study**. American Journal of Preventive Medicine 2008;35(4):357-63 |
| **DPS Follow-up** | Lindstrom J, Ilanne-Parikka P, Peltonen M, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006;**368**(9548):1673-9 |
| **DPP Follow-up** | Diabetes Prevention Program Research G. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. The Lancet 2009;**374**(9702):1677-86 |
| **PODOSA** | Douglas A, Bhopal RS, Bhopal R, et al. Design and baseline characteristics of the PODOSA (Prevention of Diabetes & Obesity in South Asians) trial: a cluster, randomised lifestyle intervention in Indian and Pakistani adults with impaired glycaemia at high risk of developing type 2 diabetes. BMJ Open 2013;**3**(2) doi: 10.1136/bmjopen-2012-002226[published Online First |
| **EDIPS (main)** | Penn L, White M, Lindström J, et al**. Importance of Weight Loss Maintenance and Risk Prediction in the Prevention of Type 2 Diabetes: Analysis of European Diabetes Prevention Study RCT**. PLoS ONE 2013; 8(2): e57143. |
| **EDIPS-Ncl** | Penn, L., et al., **Prevention of type 2 diabetes in adults with impaired glucose tolerance: the European Diabetes Prevention RCT in Newcastle upon Tyne, UK**. BMC Public Health, 2009. 9(1): p. 342. |
| **SLIM** | Roumen, C., et al., **Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study**. Diabetic Medicine, 2008. 25(5): p. 597-605. |
| **DPP** | Knowler WC, et al. **Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin**. New England Journal of Medicine. 2002; 346(6): 393-403. |
| **DPS** | Tuomilehto J, et al. **Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance**. New England Journal of Medicine. 2001; 344(18): 1343-50. |
| **Da Qing** | Pan, X.R., et al**., Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study**. Diabetes Care, 1997. 20(4): p. 537 - 544. |
| **Newcastle-IGT** | Oldroyd, J.C., et al., **Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance**. Diabetes Research and Clinical Practice, 2006. 72: p. 117 - 127. |
| **Whitehall study** | Jarrett RJ, et al., **Worsening to diabetes in men with impaired glucose tolerance ('borderline diabetes').** Diabetologia 1979. 16(1): p. 25-30. |
| **Malmo** | Eriksson, K.F. et al. **Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study**. Diabetologia, 1991. 34(12): p. 891-8. |
| **Wein Study** | Wein, P., et al**., A Trial of Simple versus Intensified Dietary Modification for Prevention of Progression to Diabetes Mellitus in Women with Impaired Glucose Tolerance.** Australian and New Zealand Journal of Obstetrics and Gynaecology, 1999. 39(2): p. 162-166. |

# CHAPTER SIX: PREVENTION OF TYPE 2 DIABETES IN HIGH-RISK INDIVIDUALS CASE STUDY ANALYSIS OF KEY FUNCTIONS AND ACTIVITIES FOR INTERVENTION DEVELOPMENT AND EVALUATION

From my review of intervention guidance models, my empirical research and the wider evidence relating to T2D preventions, I have identified key functions and activities for development and evaluation of complex interventions to improve health. I have then used these key functions and activities to structure a case study analysis of T2D prevention and intervention guidance. This analysis is presented below with key functions and activities as sub-headings.

For this analysis my hypotheses are that:

Key functions and activities for intervention development (including those described in the MRC 2008 framework, others identified from the guideline review, my empirical research or emergent from the analysis) [20] are applicable prior to each of the summative evaluation stages (efficacy, effectiveness, and implementation) described in previous models.

Key functions and activities will vary depending on the evaluation stage such that: some activities will be more appropriate at one stage than at another and how these activities are best conducted will vary between stages.

Analysis of T2D prevention as a case study according to key functions and activities will inform the design of a new intervention guidance model.

## 6.1 Evidence gathering methods

Identifying the evidence base traditionally involves a systematic review of available evidence unless there is a recent, good quality review available. [20] The function and strength of a systematic review is in providing an unbiased assessment of existing evidence. Devising a systematic review search strategy is relatively straightforward for efficacy evidence; restriction to RCT study designs, tightly defined inclusion criteria and primary outcomes allow exclusive and appropriate search questions to be constructed that will retrieve a manageable number of studies. For efficacy evaluation in T2D prevention, diabetes incidence is the clinically meaningful outcome of interest. The

DPP and DPS were both methodologically sound RCTs with T2D incidence as the primary outcome, thus appropriate for efficacy evaluation and both were identified in the Gillies 2007 review[6] and the NICE-R2.[9]

However, there are some limitations of systematic reviews of efficacy evidence as illustrated by the case of T2D prevention and the Gillies review.[6] The DPP and DPS have secondary analysis papers,[109, 112, 115, 149] follow-up studies[117, 118 113] and associated qualitative studies that were omitted from the Gillies systematic review. [6] In addition the DPS' two sister studies (EDIPS-Newcastle [submitted paper SP1] and SLIM) are contributors to the RCT evidence base,[11, 150] but were omitted as these were published later than the Gillies review and thus demonstrate the need for a review to be recent. Revisions, to update systematic reviews require duplication of effort and may be wasteful of resources or introduce inaccuracies, particularly where the evidence base is substantial.[151] Follow-up and later studies are included in NICE-R2 and associated qualitative studies in NICE-R4.[9] However the resources available to NICE are unlikely to be available to, or appropriate for, a single intervention development project.

RCT evidence is important for efficacy evaluation, where proof of principle is the important function. [152] The DPP and DPS experiences illustrate the likelihood that respondent burdens and the long-term participant commitment would limit external validity, whilst the cost and capacity to deliver these interventions restricts their utility for real world settings.[153, 154 155]

Further difficulties and limitations arise in the systematic retrieval of effectiveness evidence. In the case of T2D prevention this is exemplified in the search strategy for NICE-R3 and explained in the NICE methods guide.[9, 156] In this case, and for effectiveness studies more generally, the evidence base may be overwhelmingly extensive, study inclusion criteria may be imprecise and methodology less robust

Limitations around systematically retrieving evidence of service implementation include requirements for published, accessible and detailed evaluation, ideally including long term monitoring, that are available from situations where robust data collection and publishable evaluation may be a low priority. Furthermore, evidence utility is limited where implementation is context specific (i.e. different and specific health care systems). [20]

Review methodology is imperfect. [157] In particular there are problems associated with synthesising qualitative evidence, [158] as well as heterogeneity issues, especially in relation to intervention delivery.[159]

For evidence gathering there is also a need to consider local contextual evidence, such as might be gleaned from consultations with stakeholders (similar to 'pre-testing' in social marketing terminology)[160] that may not be achieved through a systematic review of published evidence and that may be particularly important for real world effectiveness evaluations.

As well as explaining the importance of systematic literature reviews new guidance should acknowledge their limitations. The balance between a review that is restricted by study quality (e.g. RCT evidence only) or exclusive search terms (such as pre-diabetes) and more purposeful evidence gathering that might be better suited to effectiveness evaluation should be addressed. Alternative methods of evidence finding, such as ways to incorporate local contextual evidence should be included. Discussion of appropriate methodology, dependent on the evolutionary stage of intervention development would be helpful.

- Systematic literature reviews have limitations
- Evidence gathering methods other than literature reviews, such as stakeholder perspectives, are important
- The relevance and importance of different evidence gathering methods vary according to the intervention development stage

## 6.2 Behaviour change theories and participant behaviour

Interventions to improve health at an individual level centre on enabling people to exert control over health determinants and thereby improve their own health, therefore behaviour is an important mediator. The behaviour change theory described in the DPS was based on the Transtheoretical Model and its Stages of Change construct.[161] The primary behaviour change technique (or package of techniques related to the Transtheoretical Model) was motivational interviewing; with counselling sessions delivered in individually personalised consultations.[162] In the DPS these consultations relied to some extent on the individual physical activity and dietary monitoring assessments (i.e. coding, analysis and feedback of individual food and

physical activity diaries). This detailed individual assessment and feedback is time-consuming, carries respondent burden (which may restrict inclusion by socio-economic status and affect external validity), is impractical for group delivery and not scalable for implementation. Thus, the DPS protocol clearly requires much modification for the intervention to be practical in a real world setting. As a case study this exemplifies the need for reworking of an intervention methodology that was appropriate for efficacy evaluation. Reworking intervention methodology means that key developmental activities, including assessment of feasibility and acceptability, need to be revisited prior to effectiveness evaluation.

In the GOAL effectiveness study, there was a strong focus on behaviour change theories including the Health Action Process Approach (HAPA). [163, 164] The aim to determine and describe the behaviour change processes [165] is a strength of the GOAL study and this detailed description facilitated the development of the Greater Green Triangle (GGT) study based in Victoria, Australia, which utilised similar behaviour change process methods.[134] Detailed descriptions of the behaviour change processes are important for intervention replication.[166] However, over-burdening participants with data-collection instruments could restrict participation and affect retention, particularly where there are cognitive or language difficulties. A need for balance (between comprehensive data collection and respondent burden) is applicable to guidance generally and especially relevant in developing equitable interventions for effectiveness evaluations.

- The most appropriate balance between comprehensive process data collection and respondent burden varies depending on the intervention development stage

## 6.3 Behaviour change theories and staff behaviour and motivation

Interestingly the GOAL translational study acknowledged the importance of facilitator motivation to promote intervention success. Often a pioneer research team, that is responsible for intervention development, might be highly motivated, but this cannot be assumed for all delivery centres as an intervention is rolled-out. In expanding an intervention beyond the early pioneer team,[167] facilitator motivation and ways in which this might be maintained, such as including a degree of facilitator autonomy, should be considered for good intervention design.[168] In contrast to the GOAL study

approach, the DEPLOY study protocol relied on a 16 week set of structured lesson plans extracted from the DPP curriculum.[169] This highly structured model is useful in ensuring consistency of application, but loses flexibility of approach.[168] Where the delivery relies on specially trained lay health coaches, a tightly structured paradigm has merit in providing a reliable, replicable model. The effect of this prescriptive approach on facilitator motivation and participant retention in the longer term is uncertain. There is tension between the needs for: adherence in intervention delivery; flexibility for context appropriate adaptations; and autonomy to promote provider ownership. An appreciation of this tension and options for its resolution could be expanded in devising new evaluation guidance.

- Motivation of Intervention delivery staff is important and may be affected by their degree of autonomy Tension between protocol adherence, facilitator motivation and context may affect intervention delivery

## 6.4 Design drift and protocol comparison

The intervention design drift, between individual delivery and the theory underpinning the DPS and DPP, to programmes where interventions are delivered at group level represents a major difference in protocol.[161] This may be necessary from a cost and capacity perspective, but the assumption of equivalent efficacy is unwarranted. Any added benefit in incorporating elements of social interaction, [170, 171] or evaluation of reach and inclusivity are untested. The DEPLOY intervention is described as 'Based on the DPP curriculum,' but it is not clear which components are retained in full and which have been modified. There is no DPP 'brand standard' to be achieved in order to describe an intervention as 'DPP based.' In a commercial situation branding clarifies the model and provides some guarantee of quality. The issues of intervention brand or other mechanisms to identify quality and fidelity are important for implementation, and could inform intervention guidance.

We do not know whether the intervention delivery or the behaviour change strategies used in either the DPP or DPS were optimal, only that these different intervention paradigms were similarly effective. Both the DPP and DPS included group led physical activity sessions. This intervention feature is seldom preserved in real world settings. Between study comparisons of different intervention protocols to draw out common

components in interventions of proven efficacy, is an evaluation function that could usefully be included in new intervention guidance.

- Protocol comparisons, across studies with similar research aims, could provide useful evidence

## 6.5 Incorporating concurrent advancement in related fields and technologies

Application of behaviour change strategies more broadly also evolved during the evolution of T2D prevention. Whereas when the DPS was planned specifying a behaviour change theory was best practice, we might now anticipate a more explicit pragmatic focus on behaviour change techniques.[172] One advantage of using behaviour change techniques is the opportunity to evaluate their use in intervention delivery as an outcome of interest.[173] Assessment of the behaviour change techniques used in delivering an intervention could provide a fidelity measure that does not rely on prescriptive session plans. Reviewing the concurrent evolution in understanding and application of behaviour change theory (alongside intervention development) is a more generally applicable activity for inclusion in intervention guidance.

As technology advances, new opportunities for intervention design and data collection such as accelerometer measures of physical activity[174] and electronic communication with participants become available. The opportunity to incorporate concurrent advancement of technology alongside intervention evolution would also be usefully addressed in a new guidance model.

- As interventions evolve through staged progression other technologies also evolve and provide new opportunities for intervention development

## 6.6 Modelling intermediate health outcomes

In the case of T2D prevention, the DPS and DPP participants were overweight or obese (defined by inclusion criteria, with different criteria by ethnicity within the DPP).[175] For modelling purposes the lifestyle targets, (weight loss (5% [DPS] or 7% [DPP]), dietary changes and increased physical activity) advocated in the DPS and DPP were clearly described.[169] In secondary analysis, lifestyle changes were modelled to the primary outcome (T2D incidence).[109, 110, 115]

As a candidate for modelling, weight loss can be easily and objectively measured, and a weight loss target is an assessable intermediate health outcome. Although physical activity can also be objectively measured, this was not done in either the DPS or DPP, probably due to the limited technology available at the time. Physical activity was assessed in these trials with self-report, diary-style instruments. Although a similar self-report measure, or an objective measure of physical activity, is a possible intermediate proxy for T2D incidence (behavioural outcome), it might be more convincing if supported by weight loss measurement.[109] On the other hand, measurement of dietary components is difficult. Available objective dietary measures include plasma vitamin C and carotenoids that may be useful for modelling .[91] The dietary targets in the DPS and DPP were expressed in ways that can only be accurately determined by coding and analysing individual food diaries. Dietary changes are not useful as modelling criteria.

An advantage of using intermediate health outcomes (e.g. weight loss rather than T2D incidence) is to facilitate evaluation within a shorter timescale. However the timescale for behaviour change to be embedded remains a consideration and maintenance of weight loss or physical activity increase cannot be assessed in short studies. The National Obesity Observatory (NOO) Standard Evaluation Framework suggests that where weight loss or physical activity increase are the outcomes of interest these should be assessed in interventions of more than one year's duration.[176] The GOAL study reported weight loss at 1 and 3 years of follow-up.[132, 177] Although the mean weight loss was less than reported in the DPS, the fact that this loss was maintained at three years suggests possible intervention effectiveness. The GOAL study, in common with most 'real world studies' was limited by lack of a randomised control group.

Although weight loss can be modelled to T2D incidence using DPP,[90] DPS,[12] or EDIPS[13] data this only equates to a population identified by IGT. We should not assume that weight loss would demonstrate the same preventative effect in a differently identified population.[13]

In a new guidance model the limitations associated with extrapolation of intermediate health outcome data for modelling purposes, such as where an intervention is applied to a differently identified population or where intervention protocols have 'drifted'

some way from the original efficacy study designs, should be acknowledged with an explanation that assumption of similar primary outcome effect is insecure.

- Modelling of behavioural and intermediate health outcomes may be used to reduce an evaluation timescale
- However, the limitations of modelling, relative to empirical research, should be acknowledged

## 6.7 Testing procedures: feasibility, acceptability and stakeholder perspectives

Procedures for the DPS and DPP were prescribed in detailed research protocols and were intended to provide best conditions for success with limited consideration of cost or large scale capacity to deliver.[178] In the T2D effectiveness and implementation studies analysed here, the lifestyle goals were similar to the original RCTs, but recruitment strategies, delivery mode, delivery staff, intervention content (in some cases)and primary outcome measures were all different.

In the FIN-D2D study[145] intervention procedures for high-risk individuals were based on the DPS intervention, with local, resource dependent variations.[133] The retention rate of 50% of the total cohort at one year reflects the difficulties in participant follow-up in real world settings.

The GGT study[134] used social marketing techniques and pre-testing with stakeholders[160] to develop a DPS based intervention. A similar feasibility procedure is advocated in the MRC 2008 framework (MRC case study 3 Rudlof et al 2006)[179]

The implementation of the Saxon-DPP has precisely defined management and administration structures and is delivered in community settings by 'prevention managers' who work independently and are employed by the TUMAINI institute.[147] The institute is responsible for the programme content (including provision of standardised materials), administration and quality assurance. Prevention managers receive a basic salary (30%) and performance related pay (70%). Efficient administration procedures are vital for research conduct and follow-up at any stage, but the scale of administration for implementation makes this an important issue that may not be evaluated or reported in academic literature. In addition inclusion of

performance related pay introduces a commercial approach to intervention delivery. Commercial intervention strategies could be further researched. [180, 181]

- Administration procedures are important, especially for large scale implementations, and often poorly reported
- Stakeholder perceptions are important in evaluating feasibility and acceptability

## 6.8 Determining inclusion criteria for sample size estimation

The DPS and DPP recruited adults with persistent IGT (IGT on two consecutive OGTT tests). This strategy defined a coherent high-risk population group using an objective, exact parameter that was appropriate for an efficacy trial, and allowed sample size calculation. The DPP recruitment strategy included identifying committed participants who were able to cope with data burden in order to ensure complete data collection as far as possible.[178]

The predictive sensitivity of IGT for progression to T2D within 7.5 years, in the San Antonio Heart study was 50.9% (a mean rate of 6.8% per year) [182]and in other studies rates between 4% and 8% per year, depending on the population, were reported. [183] The sample size for the DPS RCT was based on an estimated between arm difference of 35% in five years.[65] As repeat OGTT testing is time consuming, inefficient and burdensome (both in terms of cost and participant inconvenience), the OGTT is not considered appropriate for risk identification in real world situations.[9] Alternative ways of identifying high-risk individuals for real world intervention provision are needed.

The Finnish prospective risk score 'FINDRISC' can be used to identify different levels of risk for future T2D expressed as percentage 10 year risk.[72] The concise FINDRISC comprises: age, gender, BMI, waist circumference, hypertension (as drug treated hypertension), family history of T2D and knowledge of previous hyperglycaemia. It is usually completed as a self-report calculator. The standard version of FINDRISC also includes a question about physical activity and one about berries, fruit and vegetables. These last two questions are principally included to introduce lifestyle considerations for discussion rather than for their ability to add to the model's predictive power.

The FIN-D2D, translational study within the high-risk T2D prevention implementation strategy recruited on either of four high-risk measures (FINDRISC score ≥15, previous

gestational diabetes, previous ischemic event, or known IFG or IGT) and those at high-risk were referred for an OGTT to exclude prevalent T2D.[184] The GTT study recruited on the basis of the Australian AUSDRISK (which was derived from FINDRISC) risk-score tool (score >12) with blood glucose measures (IFG or IGT) to exclude T2D[104], whilst the GOAL study recruitment strategy was based on FINDRISC score ≥ 12.[185] A risk score recruitment strategy was similarly used in the DE-PLAN suite of studies, including the PREDICE study (FINDRISC ≥ 14 or FINDRISC < 14 with IFG or IGT).[186 136] The American community based DEPLOY study recruited on the basis of BMI >24 kg/m $^2$, ≥ 2 diabetes risk factors and capillary HbA1c 110 to 199 mg/dL. [97]

The Saxony-DPP, and the PREDIAS block randomised controlled trial within the Saxony–DPP, used a prospective risk score (German-FINDRISK score >10) or risk assessment according to a primary care physician followed by capillary HbA1c testing to exclude prevalent T2D.[187] Mixed inclusion criteria make sample size determination for controlled intervention with T2D incidence as a primary outcome very difficult.

An optimal and pragmatic strategy to identify high-risk individuals for the purpose of intervention where reduction in T2D incidence is the primary outcome has not been determined.[13] This evidence gap is included in the research recommendations of the NICE guidance.[9]

- Robust research study design, clear inclusion criteria and accurate sample size calculation is crucial at any stage to produce robust evidence of effectiveness and cost effectiveness

## 6.9 Assessing reach and equality

For efficacy and other controlled studies accurate estimation of sample size is important. However, reach, external validity, and equality issues may be considered less important for efficacy trials than for effectiveness studies (and are arguably unachievable). Guidance for evaluation of reach is described in the conceptual intervention guidance models MOST, which is explained as a multiphase optimisation strategy that includes screening, optimisation with factorial analysis to identify active components and refining, [188 189]and RE-AIM (Reach, Efficacy/Effectiveness, Adoption, Implementation, and Maintenance).[32] A new guidance model should expand on the relevance of different outcome variables to the evaluation stage.

- The value of an intervention is not only about the effect size, as outcome difference between intervention and control groups, but has other dimensions including equity.
- The relative importance of different evaluation dimensions will vary according to evolutionary intervention stage.

## 6.10 Choosing evaluation study design

Randomisation is the procedure that best avoids bias between intervention and control groups for evaluation. The primary outcome of interest in the DPP and DPS RCTs was T2D incidence, which is a clinically meaningful outcome, providing strong evidence of differential effect.[6] The T2D risk reductions reported in the DPS, DPP, and other similar RCTs were remarkably consistent and meta-analyses have provided review level evidence of efficacy.[6, 9] These RCTs have strong internal validity, but external validity is questionable as respondent burden and long term commitment led to self-selection.[148] The DPP had percentage targets for females (exceeded) and ethnic minority groups (under recruited), and failure to recruit to target is a limitation of this study.[148]

Weak study design, reliance on intermediate outcomes and imprecise inclusion criteria limit T2D effectiveness assessments. Modelling of weight loss to T2D incidence cannot be assumed for differently identified populations. Only the recently published PREDICE real-world effectiveness study had T2D incidence as a primary outcome measure.[102]

The large scale implementation programmes, Saxon-DPP in Germany and Victoria State Life! Programme in Australia,[104] built on these limited effectiveness studies with similar design and recruitment procedures. [190] In the Saxony-DPP the incorporation of the nested RCT could have been better used to assess the external validity if there had been a recruitment audit trail to determine the representative nature of the within service recruitment. [32]

A logical structure for deciding which evaluation designs might be most appropriate for different evolutionary stages would be a useful addition to a new guidance model.

- Individual randomisation is robust for demonstrating intervention effect, but external validity may be limited

- The most appropriate evaluation study design might vary by evolutionary stages of intervention development

## 6.11 Analysing change process

The shift of emphasis, from what will provide the best chance of intervention success (efficacy) to scalability (implementation) underlines the importance of properly analysing the change process and determining the essential active ingredients of the 'successful' intervention. There is a danger that burdensome procedures might promote intervention generated inequalities.[191]

Qualitative or other in depth evaluation of the behaviour change processes within T2D prevention trials, could have been used to modify and improve the strategies, but the scarcity of this information [9] limits the utility of the trials to inform intervention evolution. The NICE-R4 [9] review that addressed views, barriers and facilitators relating to T2D prevention in adults with IGT or IFG included a total of 14 published studies, of which only seven related to barriers and facilitators to changing lifestyle behaviours (four qualitative and three survey based).[18, 192-197] One qualitative study was nested within the DPS[195], one within EDIPS-Newcastle[18], and the other within the GOAL study.[194] This lack of process evaluation in the T2D prevention trials is a missed opportunity.

Understanding participant perspectives is important for developing the next intervention stage, and it would now be considered good practice to include trial related qualitative work as formative process evaluation.[198]

- Qualitative evaluation may inform intervention refinement between evolutionary phases without adverse impact on general respondent burden

## 6.12 Assessing cost effectiveness

To assess cost effectiveness a comparative unit used in health economics is the Quality Adjusted Life Year (QALY). [199] There are other comparative units (e.g. Disability Adjusted Life Year DALY), but the QALY is the NICE standard.[200] QALY assessment includes both cost and benefit that allows comparison of different treatments for one condition and a specific treatment for different conditions.

The utility of the QALY should be to facilitate comparison of treatments for allocation of resources, for example within the UK NHS, aiming at efficient use of limited

resources. Preventive interventions are problematic for resource allocation as prevention requires money to be spent 'up front' for health gains in the longer term. Therefore it is difficult for spending on prevention to compete equally with spending on treatments for prevalent ill health, particularly where decisions are made at a local level. In addition in the UK the recent allocation of health promotion to local government means that there are now different budgets for preventive interventions and treatment of ill health. Thus any financial benefit due to Local Government investment in preventive intervention would be reaped by the NHS. Long term prevention initiatives may require more strategic policy level funding allocations such as 'ring fenced' monies.[201]

To make a resource allocation case for preventive interventions, evidence based comparison of cost and benefit of pragmatic 'real world' preventive interventions is vital. This might include modelling of efficacy evaluations, including estimation of longer term consequences.[202] There are cost-benefit and cost-effectiveness assessments based on the DPP and DPS, although variation in the exact inclusions (e.g. does it include screening costs?) and modelling duration for outcome events in different published scenarios can make it difficult to extract the meaning and relevance to inform intervention planning.[9] There are also problems of costings in different countries and health care systems that compound the extraction of meaningful information. For meaningful analysis, the screening costs and progression rates related to baseline risk need to be included as well as adjustment for the cost and benefit of early detection and treatment of T2D (as a result of screening for risk factors). [9]

Health economic evaluation was conducted in association with the recent NICE reviews.[9, 80] However, the economic modelling for intervention in high-risk individuals was based on evidence extrapolation which included putative estimates of intervention benefit in a population with different baseline risk assessment criteria and with different intervention delivery.

In the case of diabetes prevention in high-risk individuals, where there is a clinically meaningful outcome that can be proven within a reasonable timescale, a robust health economic case for resource allocation should be possible and persuasive, but it needs a proven and practical (implementable) evidence base.

- Prevention requires monies to be spent 'up-front' for long term health gains.

### 6.13 Robust assessment of 'real world' studies is vital to inform resource allocation. Assessing cost and capacity to deliver

To provide funders with the information required to allocate investment in a preventive intervention a useful presentation of budget options would be as a business case. There is a disconnection between the economic modelling, where the output is presented as cost per QALY and the information that service commissioners and providers need. NICE has provided costing tools to help address this gap. However, even when the intervention cost per QALY clearly demonstrates cost effectiveness, implementation still depends on available resources and on decisions to allocate resources to prevention, against the demands of other services, especially demands of acute health care provision. As highlighted above, in the UK, there is also a disconnect between investment by local government for the NHS to reap rewards in terms of reduced health care costs.

- Prevention resources may need to be specifically allocated 'ring fenced'.

### 6.14 Reporting

Reporting is important across all stages of intervention development. Publication in the research literature is essential and should be included in intervention guidance.[20] Reporting of the DPS and DPP primary outcome and secondary analyses has been extensive and frequently cited.[203] T2D prevention studies have also been widely disseminated through conferences and various events including World Conferences for the Prevention of Diabetes and its complications (WCPDs).

However, publication of effectiveness studies may not be comprehensive, especially where these studies are small scale or ineffective. Publication bias favours RCT and 'new' research evidence. [204] Successful translation of efficacy research to the real-world is problematic and where these efforts fail, publication may be particularly difficult to achieve. Even when effectiveness research is published it may be excluded from a systematic review where searches are restricted by study design or key-words. For example the DE-PLAN project map (Figure 9) identifies numerous intervention centres many of which do not appear to have associated publications. The 2010 WCPD organisers invited contributions for a book, 'Diabetes Prevention in Practice.'[104] Contributors to this book were subsequently invited to revise their chapters for a

special edition of the British Journal of Diabetes and Vascular Disease.[15] There is an opportunity for high impact journals to support effectiveness research by publishing special editions in this way. There may also be an opportunity for large research funders to influence and reduce publication bias.

- Reporting is important at all intervention stages
- Journals and funders have potential to support effectiveness research through promoting publication

## 6.15 Dissemination (Roll -out)

When small scale interventions are rolled-out to larger service provision there is a danger that limited resources[205] may lead to a weakening of intervention quality. This was highlighted in reflections from the Victoria state, 'Life!' team.[206] They have identified important components of the GGT study (Individual session prior to joining the group, individual feedback on diet and physical activity diaries, feedback to participant on their blood pressure and cholesterol results at 3 and 12 months, funding for recruitment costs) that are missing from the service model. The 'Life' team have also detailed 'other wisdom gained', from their experience of expansion from the GGT roll-out study to wider service provision, among which is the advice to expand through a pilot and incremental roll-out and the need for social marketing (advertising) campaigns (run in parallel to the high-risk approach) to raise awareness of the seriousness of diabetes, risk assessment and prevention potential. [206]

- Incremental intervention roll-out may improve fidelity
- Individual and population level interventions may benefit from parallel dissemination

## 6.16 Links between programmes

The national programme in Finland included a population awareness raising strategy alongside a high-risk intervention strategy. The large-scale implementation programmes for diabetes prevention in Finland and Saxony have been instigated as top-down approaches, including both population (raising awareness) and high-risk (intervention targeting individuals) strategies. In Finland, the high-risk intervention was incorporated into existing primary care structures, whereas in Saxony the intervention provision was organised through the TUMAINI institute. High-level organisation and

funding commitment is required to accomplish such large-scale strategic approaches.[206]

- Co-ordinated approaches to large scale intervention dissemination require high-level policy commitment

## 6.17 Fidelity of intervention delivery and staff training

The GOAL study, as detailed previously, highlighted the importance of practitioner motivation in intervention delivery.[134] Successful implementation is not just about large scale plans and funding, but also about capacity, and facilitator training and commitment. Both the Life! And the Saxony projects had large associated facilitator training plans. [134, 207] The Life! authors point out the difficulty of coordinating participant recruitment rates with the availability of appropriately and recently trained intervention delivery staff. Variations in training quality could impact intervention fidelity and effectiveness

- Co-ordinated training of intervention delivery staff is vital for successful intervention implementation.

## 6.18 Surveillance and monitoring

For surveillance and monitoring of service provision to be possible in the long term, data-collection systems need to be incorporated within the programme delivery, not just as research add-ons. This is really a design issue that echoes the need for collaborative intervention development that involves both research and service providers. The Saxony programme has 'quality measures' that are evaluation outcome measures, based on individual participant data, including participant waist and blood-pressure measurement, as prescribed requirements for the programme managers to return via an online database. There is thus an emphasis on intermediate health outcomes, rather than softer measures such as 'knowledge gained' or 'intention to change' or 'fidelity of programme delivery.' There is indication of payment by outcomes achieved as a surveillance measure in this programme. However, payment (of managers) by outcomes, where outcome data is returned by the same managers would require careful auditing.

The recent publication relating to the implementation of the FIN-D2D high-risk intervention plan, [145] alongside Finland's national diabetes programme is important in

demonstrating the additive effect of multiple intervention strategies. The need for awareness raising initiatives alongside high-risk intervention provision was also identified in the Life! programme.[134, 208]

- Long-term monitoring procedures should be built into intervention effectiveness design
- Collaboration between research and service partners is needed to facilitate incorporation of monitoring in intervention design.

## 6.19 Long term follow-up

Long-term follow-up could be applied at any evaluation stage Both the DPP and DPS have reported long term follow-up evaluations.[117, 118 113]The DPS started recruitment in 1993. Different centres began recruiting at different time points and the recruitment was protracted. In March 2000, the independent end point committee recommended that the trial be ended. Following the completion of the active trial, participants continued to be followed-up with assessments, annually at first and bi-annually later. As a result there is considerable and valuable long term follow-up data from this study. Similarly the DPP has reported follow-up results at 10 years after the end of the active trial phase.

- Long-term follow-up is important at all evaluation stages

## 6.20 Summary

Review of intervention studies, which span the biomedical research continuum, for T2D prevention in high-risk individuals with reference to key activities and functions for intervention development, supports the utility of a staged evolutionary construct in intervention development and evaluation. This analysis suggests that differentiation of intervention development and evaluation strands, with defined decision points would clarify guidance and improve its utility. Summative evaluation points, efficacy, effectiveness, implementation and sustainability are appropriate to provide evidence to support decisions regarding the next stage and should be complemented by process evaluation and evidence synthesis.

This analysis of T2D prevention studies clarifies the need to repeat key functions and activities of intervention development prior to each summative evaluation point and supports the concept of variation in these key functions and activities that are

dependent on the evolutionary stage of intervention development. A model based on evolving design and redesign loops would improve clarity and also facilitate the incorporation of advances in related fields and technologies alongside evolutionary progression of intervention development. As intervention development progresses to service provision the tensions between fidelity and flexibility, reach and equity, sufficient data and respondent burden, as well as cultural acceptability, contextual adaptations, and stakeholder perspectives become increasingly important.

The analysis of T2D prevention outlined in this chapter is informed by my research experience in the field. This empirical research, which is presented in my submitted papers, provides the fundamental underpinning to the analysis. In the next chapter I reflect on this research and my experience of T2D preventive interventions, conducted at Newcastle University. I have written this as a reflection to explain the way my thinking has evolved and to clarify the pivotal role of this empirical research to my thesis.

# CHAPTER SEVEN: PROPOSED NEW GUIDANCE FOR THE DEVELOPMENT AND EVALUATION OF COMPLEX INTERVENTIONS TO IMPROVE HEALTH

## 7.1 Information to support new guidance

The guidance review, analysis of T2D prevention case studies and reflection on my empirical T2D prevention research support a need for revised guidance.

I have identified the benefit of separate intervention development and evaluation strands with progressive summative evaluation points. Separating intervention and evaluation strands facilitates optimisation of each strand.[30] Key activities of intervention development and evaluation include:

- Evidence gathering methods
- Behaviour change theories and participant behaviour
- Behaviour change theories and staff behaviour and motivation
- Intervention design drift and protocol comparison
- Incorporating concurrent advancements in related fields and technologies
- Modelling intermediate health outcomes
- Testing procedures: feasibility, acceptability and stakeholder perspectives
- Determining inclusion criteria for sample size calculations
- Assessing reach, recruitment, retention and equity
- Choosing evaluation study design
- Analysing change processes
- Assessing cost effectiveness
- Assessing cost and capacity to deliver
- Reporting
- Dissemination (roll-out)
- Links between programmes
- Fidelity of intervention delivery (adherence and competence)
- Training procedures (staff training, health champions, peer support)
- Surveillance and monitoring
- Long-term follow-up

An intervention design loop with selected activities could be employed with great benefit at each evolutionary stage, supported by formative process evaluation, to promote stage-related optimisation of intervention and evaluation strands. Redesign at progressive stages will also facilitate design updates to reflect progress in related methodology and technology.

Following intervention optimisation, a pause in the development process, such that a defined intervention is delivered as intended (per-protocol) with adequate fidelity and minimal modification, will facilitate summative testing at the efficacy and effectiveness evaluation stages. Quantitative summative evaluation is needed to test pre-defined and measurable outcomes of interest. Definitive evaluations require experimental study designs. Variations in the outcomes of value between efficacy and effectiveness evaluation will influence the choice of study design. Beneficial outcomes that were not anticipated may be evidenced from qualitative summative evaluation.

Analysis of the T2D prevention case studies suggests that effectiveness evaluation may require more than one iteration to separately evaluate important intervention adaptations. In my proposed new guidance model I have distinguished two steps in effectiveness evaluation. The first step is to evaluate intervention effectiveness on a limited scale, where the inclusion criteria are more narrowly targeted than might be equitable for service provision. The second step is to evaluate adaptations of the intervention model, that might be necessary to ensure equitable service provision (such as for different ethnic groups or for different age ranges) or that might have further potential (such as extending the intervention model to related conditions).

Following implementation of an intervention as service provision, on-going monitoring is necessary to assess intervention performance and the degree to which the intervention continues to be delivered as evaluated. At this stage a pause in intervention development is not feasible. A degree of design drift is inevitable, such that context variations in intervention provision will evolve, and thus it is important to incorporate training and monitoring procedures in the intervention design that will be retained after the formal research evaluation of effectiveness has been completed.

Monitoring, evaluating sustainability and equity are important aspects of intervention development and design for sustainable service provision. These aspects are not well

served by current guidance. It may be necessary to develop new experimental methods to address the issue of maintenance of intervention effectiveness.

Progress decisions should be made following each evaluation stage depending on the outcomes: such as demonstration of effect; fitness of the intervention for progression to the next evolutionary stage; and options for modification/optimisation, adaptation, updating, and improvement.

## 7.2 A proposed new guidance framework: the evolutionary decision tree

Having identified a need for revised intervention guidance and determined the necessary constituents and their organisation, which I suggest are required for refined guidance, I propose a new framework diagram. This framework diagram is designed to present clearly the organisation of key activities and functions of guidance for the development and evaluation of complex interventions to improve health. It is my intention that this framework diagram will be easy to assimilate, memorise and recall. To facilitate ease of recall I have used the concept of repeated developmental units or **'building blocks'** overlaid on the metaphor of an **evolutionary decision tree**. I have incorporated standard flow-chart and decision tree formats with hierarchical relationships, intra-hierarchical cycles, decision nodes and feedback loops. Familiarity of formatting is included to draw on meaningful associations to promote effective communication and assimilation. The building blocks have structural similarities at each evolutionary stage, although the most relevant key activities (as above) will vary, depending on the evolutionary stage. Building blocks for efficacy and effectiveness stages (Figure 12) are structured to **design, test** and **decide** as explained below:

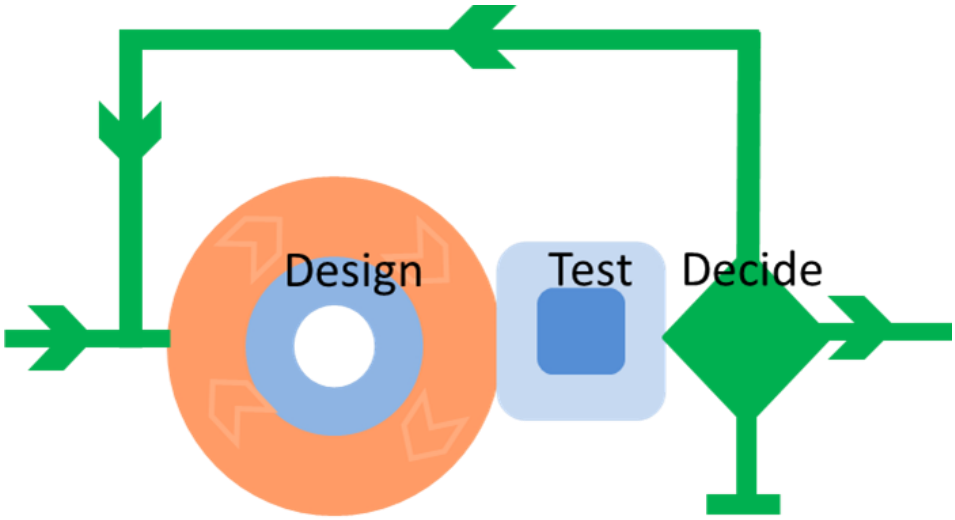
- **Design**: a design loop that has intervention development and formative (process) evaluation strands; followed by
- **Test:** a pause in intervention development for the purpose of summative evaluation, which may include both quantitative and qualitative methods; followed by
- **Decide:** a decision node where the choices are informed by the outcomes of the preceding summative evaluation and are to: proceed to the next evolutionary stage; feedback to refine the intervention before proceeding; or decide not to progress further

The building block for the implementation stage is differently structured to reflect the probability that a pause in intervention development, to allow summative evaluation, is not appropriate at this stage (Figure 13). Thus summative evaluation is replaced by monitoring procedures that run concurrently alongside a minimal intervention development strand. Implementation should be focussed on delivering an intervention of proven effectiveness with fidelity. Fidelity is about adherence to the intervention protocol and competence to deliver an intervention in a specific context. It is acceptable for an implemented intervention to incorporate minor variations to update and refresh the original design. However any radical intervention change that compromises its fidelity needs to be subjected to re-evaluation of effectiveness. In the UK, services are usually commissioned with a cycle of three or more years. If effective monitoring procedures are in place they will contribute to a decision to retain a service or to decommission at the end of a commissioning cycle. Thus a decision node is still relevant for implementation design. The implementation building block (Figure 13) is structured to **deliver, monitor and decide.**

When put together the building blocks form an intervention development and evaluation **evolutionary decision tree** that shows progressive stages. The basic stages are:

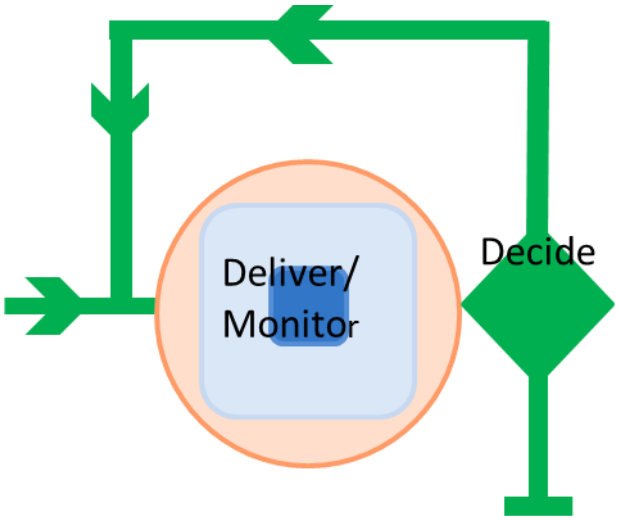
- **Efficacy:** intervention development and design and optimisation with process evaluation, culminating in a pause for efficacy evaluation
- **Effectiveness:** intervention redesign and optimisation with process evaluation resulting in a pragmatic and implementable intervention for specific 'real world' settings, culminating in an intervention development pause for effectiveness evaluation
- **Effectiveness (replication and adaptation):** context specific intervention redesign and optimisation for broader settings) culminating in an intervention development pause for effectiveness evaluation, which may be linked across intervention areas/populations
- **Implementation:** intervention implementation, with monitoring and innovation feedback, on-going evaluation of service provision.

**Figure 12: 'Design-Test-Decide': repeated unit building block of a proposed new guidance framework for the development and evaluation of complex interventions to improve health (efficacy and effectiveness stages)**




| | Key to figure 12 | Key activities and functions applicable to efficacy and effectiveness summative evaluation stages |
|---|---|---|
| Design | | **Intervention development:** evidence gathering, behavioural theory, modelling, developing procedures, reporting (arrows show this as an iterative loop for intervention optimisation prior to summative evaluation) |
| | | **Formative evaluation:** testing procedures, understanding change processes, estimating recruitment, retention and sample size, study design for the next stage |
| Test | | **Summative evaluation:** quantitative outcome assessment, process evaluation and suitability for the next evolutionary stage |
| Decide | | **Decision node:** progress to the next stage, feedback to refine the intervention and retest, outcomes do not support continuation |
| | | **Pathways:** routes available to take from the decision node with arrows to show the direction (feedback, feed forward) |
| | | **Pathways:** routes available to take from the decision node (do not proceed) |

**Figure 13: 'Deliver/Monitor-Decide' repeated unit building block of a proposednew guidance framework for the development and evaluation of complex interventions to improve health (implementation stage)**




| Key to figure 13 | Key activities and functions applicable to different summative evaluation stages |
|---|---|
| | **Intervention delivery:** updating evidence and theory, incorporating flexibility to context and minor innovations and adaptations, training and administration, linkage to policy and practice |
| | **Monitoring: fidelity of** intervention delivery: adherence and competence, relevance and acceptability to stakeholders |
| | **Evaluation of sustainability:** comparison with earlier recruitment and effectiveness outcomes, suitability to retain as a commissioned service |
| | **Decision node:** maintain commissioned service, feedback to refine the intervention and retest, monitoring outcomes do not support continuation |
| | **Pathways:** routes available to take from the decision node with arrows to show the direction (feedback, feed forward) |
| | **Pathways:** routes available to take from the decision node (do not proceed) |

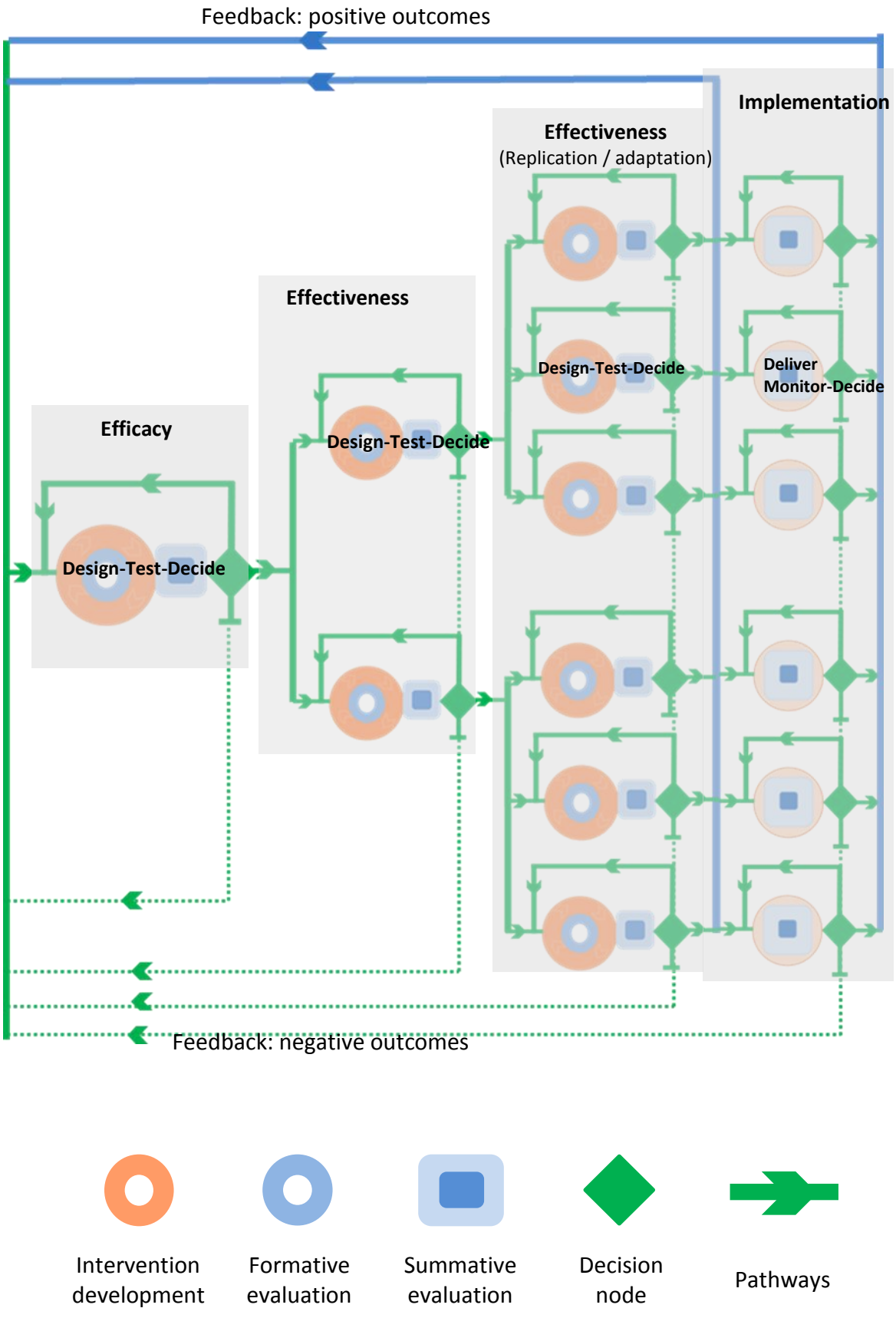
An evolutionary decision tree diagram incorporating the different stages composed of the unit building blocks is shown in Figure 14. This diagram contains some linking elements in addition to the unit building blocks. The solid green line on the left represents the underlying basic science and epidemiological evidence base, from which the initial problem identification and solution generation emerge. This baseline will also be influenced by policy and existing practice. The solid blue line at the conclusion of the effectiveness evaluation stage represents the linkage between effectiveness evaluation in different locations that feeds back to contribute to the general underlying evidence from which new initiatives may emerge. The dashed green lines represent the fact that, even when interventions do not progress, the information generated by conducting robust evaluation will feed back to the underlying evidence base and play a part in increasing knowledge that may eventually lead to a different approach.

The staged progression intervention guidance blocks, familiar to those who have used early guidance models such as the Nutbeam model and the MRC 2000 framework, are overlaid (grey boxes) onto the tree diagram. The iterative nature of development and evaluation of complex interventions to improve health is divided into within-stage 'Design-Test-Decide' loops (or 'Deliver/Monitor-Decide' loop for the implementation stage) and an overall feedback system, such that each stage adds to the evidence base.

## 7.3 Summary

Analysis of intervention guidance using T2D prevention as a case study supported a revised guidance model, which I have outlined in a framework diagram (Figure 14 below).

**Figure 14: Evolutionary decision tree diagram showing the stages in the development and evaluation of complex interventions to improve health**



# CHAPTER EIGHT: DISCUSSION

## 8.1 Principal findings

### *8.1.2 Type 2 diabetes prevention: my empirical work*

Research evidence from RCTs demonstrated the efficacy of lifestyle intervention for T2D prevention. The EDIPS Newcastle trial arm contributed to this evidence and the study results suggested that similar intervention effect could be achieved in the UK. Secondary analysis of collated EDIPS data underlined the importance of weight loss maintenance in the reduction of T2D incidence and highlighted issues regarding efficient risk identification for pragmatic effectiveness evaluation and large scale intervention provision.

Development and evaluation of the NLNY pilot study to date, in a local area of social deprivation, suggests that this intervention model is feasible and acceptable, is likely to be effective in promoting weight loss at one year, and is scalable for targeted service provision. As the NLNY intervention is based on the lifestyle change targets described in the EDIPS protocol, it is also likely to be effective in reducing T2D incidence in high-risk individuals. In the EDIPS Newcastle trial arm weight loss at 12 months was an important intermediate health outcome and predictor of reduced five year diabetes incidence in this population. However, the EDIPS Newcastle trial population comprised adults with IGT identified through repeated OGTT measurement. This risk identification procedure is not considered suitable for service provision in the UK.[9] A definitive trial evaluation of the NLNY intervention, with diabetes prevention as the primary outcome of interest is needed to demonstrate effectiveness and assess efficiency. In piloting NLNY we identified the need for intervention adaptations to promote engagement of ethnic minority communities in order to achieve equitable intervention provision. Adaptations of the NLNY intervention for ethnic minority communities need further development prior to formal evaluation.

### *8.1.2 Analysis of intervention guidance*

In this review of intervention guidance I identified bio-medical, sociological and more purpose focussed approaches to guideline development. Also I identified strengths and limitations of existing frameworks and key activities of intervention development and evaluation. The substantial evidence base for T2D prevention internationally and the

span of this evidence across the research spectrum promoted the potential of T2D prevention as a case study to inform my guideline analysis. This analysis, underpinned by my empirical T2D prevention research, informed my proposed new guidance framework. The resulting 'evolutionary decision tree framework' and its associated diagram includes staged summative evaluation of efficacy (trial of an optimal intervention under ideal conditions), effectiveness (trial of a pragmatic intervention in the real world) and implementation (monitoring and sustainability). Intervention design loops, prior to each summative evaluation stage, are proposed to promote intervention optimisation with stage relevant key activities. Following each summative evaluation necessary decision points regarding progress and feedback are included in the framework.

The position of health economic evaluation in this proposed framework is unclear. Determination of cost and benefit of lifestyle preventive intervention is particularly challenging. The staged progression concept suggests that 'does the intervention work' should precede 'will the intervention work efficiently in a real world setting.' However, return on investment is important for commissioned interventions and early indications both of likely cost benefit returns and opportunities for cost savings in intervention delivery are important.

## 8.2 Strengths and limitations of my empirical work and guideline analysis

### *8.2.1 Type 2 diabetes prevention: my empirical work*

My empirical work to date is limited by the lack of a formal effectiveness evaluation of an implementable intervention. On one hand, although efficacy of the EDIPS intervention was demonstrated, this intervention is not feasible for implementation nor efficient for service provision.[200] On the other hand the NLNY intervention, where implementation as service provision has been shown to be feasible on a small scale in one area of the UK, has not been formally evaluated for effectiveness and efficiency.

My NLNY intervention development experience has highlighted the need for consideration of context and practicalities in intervention design, alongside an evidence based protocol of proven efficacy, providing a platform for feasible and acceptable 'real world' intervention delivery. The extensive NLNY pilot work, with

associated qualitative process evaluation, strengthens the potential for a pragmatic effectiveness evaluation of an implementable and sustainable intervention model.

Although the NLNY intervention development highlighted a need for adaptation to better engage ethnic minorities, for equitable service provision, the feasibility pilot of the culturally adapted NLNY intervention is incomplete. It would be premature to plan effectiveness evaluation of the adapted NLNY intervention.

### *8.2.2 Analysis of intervention guidance*

In my guideline analysis I reviewed several previous models although this was not a systematic review. An advantage of using T2D prevention as a case study for this analysis is the extensive evidence base and span that allows the evolutionary progression of T2D prevention to be traced. However, this intervention model with a precisely defined clinical outcome is tightly focussed. Public health interventions have a much broader range and do not necessarily 'grow' from evidenced aetiological and scientific roots.

The use of three evidence sources (guidance review, T2D case study and my empirical research experience) to inform a common output contributes to the strength of the analysis. However the insight that my empirical experiences provide for the analysis should be tempered by the potential for a biased and subjective personal view. As this is my PhD thesis, the findings might be more subjective, even with the valued input from others, than would be the case had the same evidence been reviewed and analysed by an expert committee and discussed to derive a consensus. Procedures for guidance development used by NICE employ an expert committee consensus approach, however, this approach is not without limitations and may be particularly difficult in the complicated and diverse context of guideline development.[101]

Despite the extensive evidence base for T2D prevention, there is very little evidence around sustainability of service provision, or methods by which sustainability might be promoted or evaluated. This limitation of the analysis affects the proposed new intervention guidance. Similarly, although I have recognised unanticipated intervention benefits I have not expanded on methods to assess and include these in intervention guidance.[209, 210]

My framework diagram was intended to look simple. However, in comparison to earlier model diagrams, including the MRC 2000 and MRC 2008 framework diagrams it appears more complex. By using a building block concept, with standard and familiar formats common to flow charts and decision trees I sought to clarify a complex process. It is not clear whether this diagram will succeed in making guidance easier to assimilate and apply.

A framework diagram, even with detailed explanation and accompanied by a fairly comprehensive list of key activities, does not constitute complete guidance. This proposal is only a starting point for the development of new guidance and will require further analysis and testing. In particular it will be necessary to test the application of this framework to other case studies to assess its generalisability.

## 8.3 Relation to other work

### *8.4.1 Type 2 diabetes prevention*

As described previously the main T2D prevention efficacy trials recruited participants with IGT, [6, 9] whereas effectiveness studies to date have mostly used risk scores for recruitment.[9] NICE guidance advocates a risk score followed by a blood test to identify high-risk individuals.[9] However the appropriate combination of risk score values and blood test cut-points is not known. The recent decision by WHO,[63] following an earlier decision by ADA,[211] to recognise an HbA1c value (repeat measure) as a diagnostic criterion for diabetes has expanded the design opportunities for a pragmatic T2D preventive intervention. In the RCT reported by Saito et al[212] sub-group analysis suggested the utility of HbA1c to identify high-risk individuals for effective preventive intervention. However, as this trial recruited participants with IFG the utility of HbA1c as a single risk criterion remains unclear.

Most of the translational T2D preventive interventions to date have relied principally on behaviour change counselling. In a European collaboration, resulting from the DE-PLAN project, the 'European Perspective on Diabetes Prevention: development and Implementation of A European Guideline and training standards for diabetes prevention' (IMAGE) [213] a set of practical procedures have been collated and presented as an intervention toolkit.[214] A comprehensive and systematic review of behaviour change interventions for weight management, increased physical activity and healthy

eating, that was prepared for the IMAGE group was also presented to the relevant NICE PDG.[215]

The novelty of the NLNY intervention is in its experiential learning mode of delivery structured round physical activity sessions followed by reflection, with counselling and advice.[216] As both the DPS and DPP intervention protocols included group delivered physical activity sessions they contribute to the evidence base for the design of NLNY.[12, 114] The NLNY intervention may cost more to deliver than a counselling based intervention, but it is not yet clear which model would be more cost-effective.

There have been other lifestyle change interventions to address diabetes risk, apart from EDIPS-Newcastle and NLNY, conducted in the UK.[217] In the PREPARE RCT[218] Yates et al recruited ninety-eight overweight or obese individuals with impaired glucose tolerance. Participants were randomized to receive an advice leaflet, 3-hour structured education programme aimed at promoting physical activity, or 3-hour structured education with use of a pedometer. Data for seventy-four percent of participants were analysed at 24 months of follow-up. A statistically significant reduction in 2hrPG of −1.6 mmol/l (−0.4 to −2.7) was seen in the pedometer group compared with the control group, but no significant difference in the education-only group. Larger studies, 'Let's Prevent' and 'Walking away' based on a similar educational model are under way.[219, 220]

A different small intervention trial based on motivational interviewing sessions to promote lifestyle change reported in 2008. [221] Exercise was assessed by self-reported questionnaire and showed a non-significant increase in the intervention compared with the control group at six months of follow-up**.** In the Pro-Active trial of an intervention to promote physical activity targeted to sedentary adults with a parental history of T2D, [222]there was no significant difference in physical activity at one year of follow-up between intervention and control groups.[223]

Recruitment to a large trial, The Norfolk Diabetes Prevention Study [224] based on fasting plasma glucose (IFG) (and now including a large HbA1c only sub-group following a protocol amendment) to define 'pre-diabetes' is currently underway. The intervention relies on group based counselling with mentor support to promote increased exercise and healthy diet. Participants are recruited via primary care and

pharmacies. For recruitment IFG may not be the most efficient option.[212] In sub-group analysis Saito et al found no intervention effect in the isolated IFG sub-group.

Primary prevention of T2D is an alternative approach to screening for early detection of T2D for the purpose of preventing the development of disease complications including CVD. In this respect the recent findings of the ADDITION trial that aimed to assess the effect of a T2D screening programme, with intensive multifactorial treatment for those diagnosed with T2D, on mortality are relevant.[78] The response to screening invitations was high at 73%, but the authors did not find a significant reduction in CVD, cancer or diabetes-related mortality as a result of the intervention. This is an important study in that the findings may support the need to consider intervention at an earlier time in the T2D trajectory. Screen detected diagnosis of diabetes occurs when hyperglycaemia related beta-cell and vascular damage is already probable, which limits the potential for secondary prevention.[78, 225] It is likely that remission of beta-cell damage would involve extreme lifestyle change that may not be sustainable[58] and initiating less extreme intervention that might be easier to maintain at an earlier stage may be a better approach. However any beneficial effect of T2D preventive intervention on CVD outcomes is yet to be determined.[226]

An intervention based on the GTT intervention protocol, targeted to people at increased risk of CVD has recently been developed.[227]

### *8.3.2 Analysis of intervention guidance*

To what extent developments of newly proposed intervention guidance has built on the review and analysis of previously proposed intervention guidance is not always explicit. The paper by Campbell N et al[30] is one exception. The authors analyse the MRC 2000 framework [19] using case study examples and specifically state their intention to focus on early stages of intervention design. Similarly Ogilvie et al present their translational framework[41] as resulting from a case study of public health research in the UK and the Cooksey report.[10] The PRISM model development was informed by examination of existing models, identified from a literature review, and authors' experience. It is built on key elements of previous models.[32, 228]. The model of diffusion in service organisations by Greenhalgh et al [37] is described as being derived from a systematic review of empirical research studies in health service delivery. In this

analysis I have sought to examine the historical evolution of guideline development with a focus on models summarised in framework diagrams.

Many of the intervention guidance models are supported by case study analyses. As an example the MRC 2008 framework uses 14 case studies.[20] Case studies 1,2 and 3 relate to the key early developmental elements, case studies 4 to 9 inclusive are primarily about study designs for evaluation, case study 10 focusses on understanding processes, 11 is about economic evaluation, 12 is about implementation issues, 13 about reporting and 14 about involving users. Thus, these case studies are used to illustrate specific key elements in isolation. By contrast, my analysis, using T2D as a case study, relates to all key elements described in the MRC framework across sequential intervention development and evaluation stages. This broader analysis has the strength of coherence, but the limitation of a tightly defined focus.

## 8.4 Implications for policy, practice and future research

### *8.4.1 Type 2 diabetes prevention: policy and practice*

The diabetes world-wide pandemic highlights the importance of healthy lifestyles and the need for pragmatic and effective diabetes prevention.[2] A rise in longevity needs to be accompanied by an extension of healthy life years for the benefit of individuals, their health services, societies, and economies. For health service commissioners to confidently invest in preventive interventions they need resources to commit to successful programmes and evidence to justify the expenditure. Where commissioners see local need and interventions that 'seem to work' they may be reluctant to invest in effectiveness evaluation.[229] Similarly where allocation of monies to treatment of current disease conditions competes with allocation of spending for preventive initiatives difficult choices are inevitable, especially at a local level.

In the UK the NHS is over-burdened with people who are already suffering ill health. It seems opportune therefore to engage community services in the provision of interventions for primary prevention of chronic disease conditions. The move of public health to local authority responsibility should theoretically facilitate this shift.[230] However, current severe cost-constraints on local authorities mean there is a danger that the supposedly 'ring-fenced' budget meant for public health will be side-tracked to fulfil budget shortfall in non-health areas.[201] Local authorities are not the primary

beneficiaries of cost saving through investment in disease prevention. The NHS is the beneficiary of reduced treatment costs. National policy makers urgently need to take a long term cross-sector view to ensure investment in prevention of non-communicable diseases and well-targeted research investment to obtain robust evidence.

### *8.4.2 Type 2 diabetes prevention: my empirical work and future research*

Through working with service partners we have developed an evidence based and pragmatic T2D preventive intervention that is currently commissioned in the local area where it was developed.[16] Evaluation of this intervention for effectiveness and efficiency is needed. Designing a study to achieve this, without losing the essence of the intervention is challenging. For a well conducted trial precision of participant inclusion and exclusion criteria are needed to support a sample size calculation. The additional burden of research data collection alters the intervention delivery, thus introducing tension between adequate data and minimal respondent burden and there is tension between the precision with which an intervention protocol is defined and allowance for staff autonomy.[20 134] Also evaluation of lifestyle intervention is complicated by control group assessment and data collection that alerts them to beneficial lifestyle changes.[90] This is different from drug RCTs, which are likely to be placebo controlled and blinded.

We are currently progressing plans for an effectiveness evaluation of the NLNY intervention. Initially this will involve evaluation of the original version of the NLNY intervention that principally engaged the local white population. The most likely evaluation study design will be a cluster RCT to incorporate the community based recruitment that is an inherent part of the NLNY intervention model. We anticipate that effectiveness evaluation of the original NLNY intervention will be followed by further effectiveness evaluation of the NLNY adaptation for ethnic minority participants and those with previous gestational diabetes.

In principle an adaptation of the NLNY intervention may also have potential for secondary prevention of diabetic complications. This is an important avenue for future research because any risk assessment procedure designed to identify high-risk individuals is also likely to uncover those with undiagnosed prevalent T2D and there are ethical concerns regarding restrictive provision of intervention opportunities to primary prevention.

Effective lifestyle intervention for T2D prevention is likely to promote additional collateral benefits for the health of participants and others within their sphere of influence, such as children and grandchildren. It may not be possible to fully include these benefits of lifestyle intervention in a cost-effectiveness evaluation.

### *8.4.3 Guideline analysis: policy and practice*

Clearer guidance for developing and evaluating complex interventions to improve health could be productive in ensuring more realistic and well developed research proposals for evaluating intervention effectiveness and efficiency. In particular a staged building of evidence from efficacy evaluation, via small scale and tightly targeted effectiveness evaluation, with substantial feasibility piloting at each stage should lead to more efficiently allocated research resources. If an intervention effect is already proven in ideal conditions (efficacy evaluation),[26] then demonstration of intervention effectiveness is theoretically possible. The emphasis in effectiveness evaluation is then on developing a commissionable intervention, which is likely to involve partnership working that includes commissioners and delivery staff, as well as constructing a robust effectiveness evaluation study. Policy makers and funders have the power to drive research with evaluation of pragmatic and sustainable intervention programmes by targeting research resources.

### *8.4.4 Guideline analysis: future research*

A framework diagram, even with accompanying explanation and a fairly comprehensive list of key activities, does not constitute complete guidance. This framework diagram is only a starting point for intervention guidance and will require further development and testing. In particular my proposed framework has been built on review and analysis of previous guidance supported solely by T2D prevention case-studies. It will be necessary to test this framework with other case-studies to assess its generalisability.

My proposed framework diagram was designed to be simple to interpret, but it is not clear whether this framework would succeed in making intervention guidance easier to apply.

The principle that new guidance development should be built on the review and analysis of existing guidance is an important pointer for further research in this area.

# APPENDIX A: PREVENTION OF TYPE 2 DIABETES IN ADULTS WITH IMPAIRED GLUCOSE TOLERANCE: THE EUROPEAN DIABETES PREVENTION RCT IN NEWCASTLE UPON TYNE, UK.

# APPENDIX B: IMPORTANCE OF WEIGHT LOSS MAINTENANCE AND RISK PREDICTION IN THE PREVENTION OF TYPE 2 DIABETES: ANALYSIS OF EUROPEAN DIABETES PREVENTION STUDY RCT.

# APPENDIX C: TRANSLATING RESEARCH EVIDENCE TO SERVICE PROVISION FOR PREVENTION OF TYPE 2 DIABETES: DEVELOPMENT AND EARLY OUTCOMES OF THE 'NEW LIFE, NEW YOU' INTERVENTION.

# APPENDIX D: FEASIBILITY, ACCEPTABILITY, AND OUTCOMES AT 12 MONTHS FOLLOW-UP OF A NOVEL COMMUNITY BASED INTERVENTION TO PREVENT TYPE 2 DIABETES IN ADULTS AT HIGH RISK: MIXED METHODS PILOT STUDY

# APPENDIX E: PARTICIPANTS' PERSPECTIVES ON MAKING AND MAINTAINING BEHAVIOURAL CHANGES IN A LIFESTYLE INTERVENTION FOR TYPE 2 DIABETES PREVENTION: A QUALITATIVE STUDY USING THE THEORY DOMAIN FRAMEWORK

# APPENDIX F: PREVENTION OF TYPE 2 DIABETES

# APPENDIX G: ASSESSMENT OF DIETARY INTAKE: NUGO SYMPOSIUM REPORT

# APPENDIX H: TOWARDS THE TRANSLATION OF RESEARCH EVIDENCE TO SERVICE PROVISION: EXPERIENCE FROM NORTH EAST ENGLAND, UK

# APPENDIX I: STUDY CHARTS FOR ILLUSTRATIVE T2D PREVENTIVE STUDIES AND SUBMITTED PAPERS

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