

Designing and Undertaking a Health Economics Study of Digital Interventions

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Abstract

1. Scope

This paper aims to discuss some of the key issues in the economic evaluation of digital interventions, in order to stimulate debate so that the existing economic techniques may be refined or new methods developed. The paper does not seek to provide definitive guidance on appropriate methods of economic analysis for digital health interventions.

2. What are the unique issues raised by digital interventions within that scope?

Digital health interventions may be best characterised as a complex intervention in a complex system. Some digital health interventions may hold special characteristics that require non-standard methods of economic evaluation, either in terms of general study design, and wider measurement of costs and benefits.

3. What are the key challenges?

Key challenges relate to having an evaluation method, or system, that is sufficiently flexible that it can adapt to the changing nature of a digital health intervention, and can encompass interaction effects between the intervention and the wider environment.

4. What are the potential solutions?

To be further developed within the paper but at this stage it seems likely that economic evaluation of digital health interventions should consider the collection of system-level data as well as adopt a perspective to encourage wider measurement of costs and benefits than is conventionally the case with respect to evaluation of medicines, devices and procedures.

5. What are the remaining dilemmas and research agenda?

To be developed and mapped out further using case studies that will be introduced in the next draft.

Background

The aim of economic evaluation of digital health interventions is to inform decision-makers about the relative value for money of that intervention against its next best alternative. With resource scarcity, it is argued that more efficient use of resources will flow if resources are allocated to those interventions where the magnitude of additional benefits relative to the magnitude of additional costs is greatest, subject to an identified budget constraint.

To help in this task, several sets of guidelines for the design and conduct of economic analysis exist for economic evaluation studies in health care (e.g. ISPOR Task Force, Value in Health 2015), but the extent to which these have been applied in a consistent fashion for digital health interventions has not yet been studied. For instance, to the best of our knowledge, there are no existing reviews of published economic evaluations of digital health interventions, although the evidence base is clearly growing at a level that may permit such a review to be conducted in the near future. In telemedicine and telecare, which may be component parts of some digital health interventions, systematic reviews of reviews highlight considerable diversity in findings, although the overall conclusions are that there is a lack of knowledge and understanding regarding costs and therefore cost-effectiveness (e.g. Ekeland 2010; Mistry 2011), and that these mostly arise through lack of methodological rigour within the original published studies (Mistry 2014).

The paper does not seek to provide definitive guidance on appropriate methods of economic analysis for digital interventions, but instead aims to highlight what we judge to be some of the key issues in the economic evaluation of digital interventions, in order to stimulate debate so that the necessary economic tools and methods may in due course be developed. The paper is organised along the following lines. First, we describe existing guides and analytical frameworks that have been suggested for the economic evaluation of interventions applied to complex interventions. Second, using selected examples of digital health interventions, we assess how well these interventions map to these in terms of study design. Third, and finally, we propose key decision points in the design and conduct of economic evaluations in this area.

Existing Analytical Frameworks

1. ISPOR Good Research Practice Guide

To enhance the conduct and reporting of trial-based economic evaluation studies applied to new medicines, medical devices and procedures, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has recently published an updated version of their good research practice guide (Ramsey et al 2015). The guidance re-emphasises the need to base economic evidence on effectiveness rather than efficacy, the benefits from direct data collection on resource use and health states (or other measures of effectiveness) from study participants rather than indirectly (such as mapping) and the importance of recognising that study design such as randomised controlled trials (RCTs) are complementary to model-based evaluations. These recommendations appear salient for the evaluation of the digital health interventions. For example, as also argued in a companion paper (Murray et al 2016), there is recognition that RCTs are not always appropriate as a means to establish effectiveness, and a similar argument holds for evaluation of cost-effectiveness.

In some specific areas however, the recommendations may be less appropriate for digital health interventions. For example, where interventions are designed in order to bring about health behaviour change, it can be argued that they differ from medicines, devices and procedures in terms of their intended mechanisms of action. Here the notions of mechanism of the actions of effects being confined to biological interactions within single individuals have been significantly developed and refined, to accommodate importance of their interaction with the health and social care system, or indeed the wider social environment.

One area in particular where there may be a need for a different approach relates to the use of intermediate (surrogate) measures of benefit. The ISPOR Guide recommend that use of “intermediate (or surrogate)” measures should be avoided in the measurement of benefit wherever possible. However, when the expected effects of an intervention are only likely to be observed in the long-term, the Guide suggests that

surrogate measures may well be appropriate, as long as the relationship to “final” measures, e.g. mortality, health related quality of life, or well-being, is firmly established. However, even a focus on surrogate measures may not be sufficient in circumstances where the intervention is expected to adapt and change over time, and where effectiveness and cost-effectiveness is theorised to closely related to the system or environment in which it is placed. In short, existing guidelines such as the ISPOR Guide, which are available for medicines, devices and procedures, may fall short for some digital health interventions.

2. MRC Framework for Complex Interventions

Digital health interventions in some circumstances may be best characterised as a complex intervention in a complex system (Hawe et al 2004, Shiell et al 2008, Hawe et al 2009). Within the MRC Framework for the Evaluation of Complex Interventions (Craig et al 2008), a complex intervention is one that “contains several interacting components, and other characteristics, such as the number and difficulty of behaviours required by those delivering or receiving the intervention”. This creates of course a challenge in establishing which component or set of components are driving the effects that are observed. Complexity may also refer to property of the system in which an intervention is implemented, as well as the intervention itself. Shiell et al (2008) notes that “a complex system is one that is adaptive to changes in its local environment, is composed of other complex systems, and behaves in a non-linear fashion (i.e. change in outcome is not proportional to change in input)”. Petticrew et al (2013) outline this further by drawing distinctions between intervention complexity, outcome complexity and causal pathway complexity as follows:

- **Intervention complexity:**
 - Multiple, interacting components
 - Likely to be tailored, adapt or change over time
- **Outcome complexity:**
 - Spillovers and externalities, i.e. outcomes go beyond the immediate recipient of the intervention, such as influencing the behaviour or health of other family members

- Feedback loops, i.e. the uptake of the intervention may be affected by uptake by others, “social contagion” effect
- **Causal pathway complexity:**
 - Multiple moderators and mediators of the relationship between intervention and outcomes, in particular strong influence of system characteristics (i.e. the setting/context of the intervention is important and likely to generate heterogeneity in costs and benefits, through differences in resource availability, culture, beliefs, attitudes, interpersonal relationships)
 - Non linear relationships between intervention resource inputs and multiple outputs, “phase” changes, i.e. sudden, unpredictable tipping points

The key question is the extent to which digital health interventions map to the above types of complexity. It is clear that some digital health interventions may align with the above classification more than others; for example, consider a health app for the management of type 2 diabetes - if additional input on the part of health care staff is required according to individual patient goals or preferences, or if the intervention partly comprises an element of feedback from health care staff or information exchange with other users, then it may be useful for economic evaluation purposes to classify this as a complex intervention. Conversely, other digital health interventions for the same condition may exhibit little or no complexity, if they require little or no interaction with health care professionals or other recipients.

Taking forward these notions of complexity, Shiell et al (2008) draw out some lessons for economic evaluation; it is argued that, where a complex intervention lacks significant interaction with the setting, i.e. where the causal pathway is relatively simple, then perhaps they can be considered as black boxes and current methods of economic evaluation might be sufficient, i.e. identifying, measuring and valuing resource use and weighing that against the value of health or other outcomes that are produced. However, where there is significant interaction with setting, there are potentially additional challenges for economic evaluation. These challenges include more difficult choices regarding what measures of effectiveness should be included, how the consequences should be valued, and how evaluation should be conducted. These challenges may lead therefore to the need to conduct what might be termed a complex economic evaluation, e.g. attempting to estimate cost-effectiveness for

various sub-groups of patients according to the extent of their interaction with the system in question. However as highlighted by Petticrew et al 2013, in the context of systematic reviews, it is still legitimate to conduct “simple” evaluations of complex interventions, by addressing “simple” questions, (e.g. what is the average change in health after intervention receipt, relative to usual care?). In these situations, existing guidance such as the ISPOR Guide may well suffice. Ultimately, the type of evaluation conducted will depend on the research question, the level of interaction between intervention and system/setting and the importance this has for generating heterogeneity in costs and benefits, and the needs of the research user. .

Whether simple or complex, a key factor in the design of an economic evaluation of any intervention relates to judgement regarding the time frame for the expected effects to occur. This creates a challenge for digital health interventions, as the content of many interventions may evolve over time, and there may be a protracted period before benefits are observed. conventional, “simple” approaches to effectiveness and consequently to cost effectiveness within existing evaluations of digital health interventions have usually been built on the randomised controlled trial. The RCT is designed to determine whether the relationship between a constant (the independent variable), and the outcome of the interaction it has with the environment or situation into which it is applied, is free from bias and that the interaction between the independent and the dependent variable is as un-confounded as possible. So long as the intervention is constant, then this is appropriate and has been highly successful. But many digital health interventions are by their very nature not constant, with many evolving while they are being implemented. As a result, the artificial nature of many trials may mean that they are not good vehicles to indicate the potential success of digital health interventions.

If trials with randomisation at the individual level may not always be appropriate, what then are the alternative options? Aside from cluster-randomisation, other study designs such as natural experiments offer a potential opportunity (Sanson-Fisher et al 2014). For example,

the five test bed sites within NHS England may provide a vehicle to examine effectiveness and cost-effectiveness on a large scale (<http://www.england.nhs.uk/wp-content/uploads/2015/03/test-bed-prospectus.pdf>). However, the use of quasi-experimental or observational study designs to demonstrate effectiveness for economic evaluation purposes also carries with it limitations, such as the problem of being unable to control for the influence of unobserved variables (REFS). A more fundamental issue is that in many cases an evaluation will be needed by decision-makers before the digital intervention has been trialled, and in cases where a trial does proceed, by the time it is nearing completion, both its effectiveness and cost effectiveness will already be 'known' with sufficient accuracy before real-world data is available. This may then provide disincentives for the future use of real-world data to examine effectiveness and cost-effectiveness. This suggests that a decision-theoretic approach will be required (or may be sufficient?) in some circumstances, such as where the intervention could not conceivably cause harm, and where the likely effect size would produce an estimate of cost-effectiveness that is well below currently acceptable thresholds (Threlfall et al 2015). For example, the PRIMIT handwashing intervention was designed for use in a flu pandemic; in this context, international dissemination of a fully automated digital intervention which reduces the spread of respiratory infection would be likely to result in healthcare savings and wider health and socio-economic benefits so great that the cost of the intervention becomes negligible.

Within the framework of complex interventions in complex systems, a critical factor that may drive effectiveness may be the extent of uptake by a social network or other relevant population. The argument here is that changes in the relevant health behaviour can be spread or transmitted from one individual to another within a particular social network; the parallel is earlier work on obesity and the idea that this is partly a social disease, through a clustering effect (Christakis & Fowler 2007). In a similar fashion, the effectiveness and cost-effectiveness of digital health interventions may depend on diffusion through social networks for uptake and effect. For example, an internet-delivered handwashing intervention was shown to result in reductions in respiratory infection in the user and also in family members who had not engaged with the intervention directly, and one can assume smaller effects spreading more widely, due not only to the reduction in infectious contacts from the user, but also due

to handwashing behaviour by the individual in their social network. In addition, there may be feedback loops and potentially non-linear relationships, such as effectiveness at the individual level being partly dependent on nature of uptake at the group level (for example 'The GCC challenge' www.gettheworldmoving.com).

Since Christakis Christakis & Fowler 2007 there has been an explosion of epidemiological studies using social network analytical methods for describing and understanding these social network effects (for example, see Powell et al 2015).

However, there have been far fewer published attempts to use such methods as the basis for the design and evaluation of digital health interventions (Leroux et al 2013; Frerichs et al 2013). The MRC framework for evaluating complex interventions may provide an appropriate structure, placing models of theory, process and outcomes at the centre of a cycle of intervention design, evaluation and redesign. However, the framework recognises the need to expand the range of experimental /comparative designs. With the development of experimental methods in social networks analysis still at a relatively early stage (El-Sayed et al 2012).

), there is therefore ample scope for methodological development in health economic applications of social network analytic methods. A possible starting point may be a critical review of existing interventions and development of novel case studies in this area. For example, an ongoing EU collaboration, INTEGRATE-HTA (www.integrate-hta.eu) is examining aspects of complexity relevant to complex interventions in complex settings. Many of these aspects are potentially relevant when considering DHIs; including the impact of multiple interacting agencies involved in the intervention and the wider system, problems with defining the intervention due to characteristics like flexibility, tailoring, self-organization, adaptivity and evolution over time, and issues of historicity or path dependence, whereby the evolution of the system through series of irreversible and unpredictable events means that the generalizability and repeatability of an intervention is problematic.

Implications of Applying The Complexity Framework for Economic Evaluation of Digital Health Interventions

Digital interventions have been used to do a variety of different things including to promote and support healthy behaviour, to be a source of information, to improve self-management of illness, including treatment adherence, to assist in monitoring of symptoms and delivery of treatments, and for general health and clinical education and implementation of best practice care. It is highly likely that as technologies evolve and commercial opportunities manifest themselves a great many other uses will be found for these digital interventions. Each of these uses has different objectives, different outcomes, and different mechanisms of action behaviourally. This suggests that applying conventional, standard methods of economic evaluation, such as cost utility analysis, as if the intervention in question is to all intents and purposes similar to a pharmacological agent, may well not be optimal in situations of complexity. This has implications for the cost side as well as for the benefit side of economic evaluation, and also major challenges for selection of the appropriate modelling framework, outlined below. These relate to issues regarding *inclusion of development costs, measurement of health –related quality of life, and the appropriate modelling framework.*

1. Inclusion of development costs plus maintenance & running costs, or only the latter?

The vast majority of costs are incurred during development. Development costs may include:

- Literature reviews, summarising available evidence on:
 - the condition addressed by the DHI (causes, treatments);
 - Interventions likely to be effective if delivered digitally (e.g. tailored content, behaviour change techniques, emotional support);
- De novo research identifying user “wants and needs”
- Costs of content development (in an academic setting, this is usually RA time + clinical input + health psychology + other disciplines as needed)
- Costs of design features (navigation, images, videos, graphics)
- Costs of software features (interactivity, algorithms, tailoring)
- Costs of user experience testing

These costs can be quite substantial, varying according to the complexity of the DHI, but may well range from £20,000 (for a simple one session intervention) (Little et al 2013) to £500,000 (or more) for a longitudinal, highly interactive intervention with extensive content, tailored to many different variables (Yardley et al 2014). Much of these costs relate to iterative development and evaluation of the intervention to maximise acceptability and feasibility, (Yardley et al 2015).

In contrast, maintenance costs can be very low. The minimum maintenance cost is hosting. Costs of hosting vary according to complexity of DHI and levels of security and response times required, but can be as little as £200 pcm.

There are three additional considerations:

- Most DHIs require regular updating to remain “the same”, e.g. where the DHI promises to deliver up-to-date information. Updating is required for: a) content; b) navigation and visuals; and c) software. As mainstream software manufacturers update their products, DHI that are not updated will cease to function.
- As outlined in the companion paper on engagement (Yardley et al 2016), there is good evidence that that DHIs alone are often not as effective as DHI + human support or facilitation, where the human input focuses on getting the patient (user) to use the DI as intended. Unlike all other costs associated with DHI, which are fixed, these facilitation costs are variable costs as they will increase with each additional user.

- Interventions are likely to evolve unpredictably over time. Such change makes reproducibility more challenging, and also may make data collection for costs extremely difficult if the change is quick and no measurement of resource use consequences was planned or undertaken. Change may also be planned as part of the intervention, as noted above, outside of the study period. It is important that this knowledge is built into the cost estimates, otherwise there is a danger that the costs incurred in a research study may not be fully reflective of resource use outside of that setting.

Commercial companies will roll up the costs of development and maintenance, and work out a cost to users which covers these (equivalent to the cost that drug manufacturers charge for a given drug). But in the new and rapidly evolving market of digital health interventions it can be extremely difficult to determine a realistic charge that will cover the costs of development and maintenance, since the likely reach of the product and the future costs of updating it as technology changes are both highly unpredictable, and likely to be affected by future changes in how digital interventions are regulated, accredited and purchased. Where the digital intervention will be deployed in a large, known population (such as users of a national service or large insurance company) it is easier to calculate realistic costs and cost-effectiveness for providing a digital intervention at scale. An enduring issue is the question of when it is appropriate to include developments costs. They are not directly included in NICE Appraisals of medicines, but they are indirectly reimbursed through the price charged by a manufacturer. The key consideration here is likely to be whether the evaluation is conducted from a payer perspective, societal perspective or some other perspective. In some circumstances, e.g. from the perspective of a national health regulator such as NICE, the decision may be whether to develop a digital health intervention de novo and make it available as a public good, i.e. once it is provided to at least one individual, it can be provided to an unlimited number of other people at no further cost, e.g. a health app to collect individual data could be regarded as a public good. Fixed costs of development, storage, data retrieval, and encryption would be required, and the payer (the NHS) would agree a sufficient price with the manufacturer to cover these costs, together with a potential mark-up to protect intellectual property. Other perspectives than those of a national regulator can be

adopted, and other factors, such as whether the intervention is an existing product, may have implications for the inclusion or exclusion of product development costs within the evaluation.

Taking both fixed and variable costs together, the marginal costs per additional user will tend to zero as the population size increases – so one important implication is that it is critical to have a good understanding of the realistic population size likely to receive and use the intervention in real settings, rather than the number of participants enrolled in a particular research study. This is not a trivial task, requiring additional effort and data analysis (Lanham et al 2013; Ling 2012; & refer to data paper here in this issue).

2. Is measurement of health-related quality of life sufficient?

The measurement of benefit should relate to the purpose of the individual technology – what is it trying to achieve over a particular time frame? – as that acts as the key guide to how benefits are measured. The standard main categories of benefit within economic evaluation include the following:

- health effects in their natural units, e.g. % level of cholesterol reduction;
- non-monetary valuation of healthy time and/or other outcomes, e.g. Quality Adjusted Life Years (QALYs);
- monetary valuation of healthy time and/or other outcomes, e.g. willingness to pay to gain % increase in healthy life years;

Less common approaches include measurement of changes in well-being effects, although there is a growing literature, especially in the field of social care, e.g. measures of capability, the extent to which an individual feels it is possible for them to live a meaningful life, or measures of life satisfaction, are now becoming more common (Al-Janabi et al 2012).

It is clear that many different interventions are designed to achieve different objectives , some of which may relate to reductions in service use. For example, a number of DHIs have been developed for chronic conditions, such as diabetes and patients receiving warfarin, and are intended to reduce the need for monitoring visits with NHS staff. Outcomes have been measured as change in utilisation of health care resources, patient satisfaction with the service and maintained control of symptoms. For such DHIs it seems plausible to maintain an NHS perspective for costs and outcomes, i.e. only health effects and NHS&PSS costs may be deemed relevant for evaluation. (However, even here, taking a more holistic perspective, telehealth interventions for the purpose of monitoring symptoms commonly have additional patient benefits such as an increased patient reassurance and empowerment – or disbenefits such as anxiety and intrusiveness). For other DHIs however, the range of benefits may be much wider and individual health effects may take a long time to occur. These include internet based programs and apps aimed to encourage a lifestyle change, such as weight loss, exercise or sleep behaviour. While some of the benefits may constitute a change in health, others may include greater social inclusion (see GCC example above) and productivity changes.

Finally, an important issue relates to safety. There may be the potential for both intentional and unintentional harms. For example, digital apps helping individuals to commit suicide or those that provide advice that is opposite to existing guidelines are available, and so there is a clear role for national regulation here, as opposed to evaluation. Where harms are unintentional, for example, if they could lead to additional anxiety, or despondency, then it is important that these are captured in the evaluation.

3.Appropriate modelling framework

Finally, there is the challenge of bringing costs and benefits together in the appropriate modelling framework. In order to conduct evaluation that accounts for the degree of complexity that is relevant to the intervention and setting, it is vital that economic modellers develop or apply tools to encapsulate individual and population level interactions, issues of health differences in populations and the vagaries of human psychology It is imperative not to default to simplified and unhelpful assumptions or heuristics about the nature of human

behaviour (even if policy makers do regularly default to such a position!). These models and the techniques to develop them must be embraced in any kind of attempt at economic analysis of digital health interventions. In this context, there appears a role for agent-based modelling (e.g. Chalabi & Lorenc 2013; Maglio & Mabry 2011). Within this approach, individuals can be modelled to make decisions autonomously as well as interact with other individuals and with their environment using individually tailored “behavioural rules”. These rules can be non-linear (e.g. discontinuous) and time-dependent (e.g. agents adapt and learn from previous experience).

Key Decision Points in the Design & Conduct of Economic Evaluations for DHIs

There is considerable scope for variation in how a particular intervention is delivered to a potential user, and the way in which that user then interacts with that intervention and the wider environment. Moreover, feedback mechanisms may be critical to the success of that intervention, such that the wider environment has a strong effect on how a recipient uses a particular intervention. In short, some digital health interventions may be best characterised as a complex intervention within a complex system, and within the class of complex interventions, they may hold special characteristics that require the following questions to be prioritised when one designs and conducts an economic evaluation:

- Is the intervention complex? i.e. does it involve interaction with other care professionals and/or an individuals’ social network? What outcomes are expected from the intervention, if it proves to be effective? Is the causal pathway from intervention to outcomes a complex one? i.e. is there significant interaction between intervention and setting,
- Is a complex economic evaluation appropriate? (e.g. can the research question be addressed using “standard” methods of economic evaluation which do not require modelling of patient-system-network relationships to generate robust cost and benefit estimates?)

- What role should economic analysis play in the design of digital interventions? (e.g. example, should measurement of individual preferences for the characteristics associated with different digital interventions be sought prior to development, or sought in evaluations of such interventions?)
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- What costs should be included in an economic analysis for the given study perspective? (e.g. should all the resources used in the development of the digital interventions be included? Alternatively, is it acceptable to focus solely on measurement of the health care resources and any other resources required in future maintenance and support of digital interventions?).
- What benefits should be included in an economic analysis for a given study perspective? (benefits are likely to be multi-faceted and potentially span beyond health, creating a challenge for measurement, e.g. does engagement with digital interventions facilitate future employment prospects for some individuals? Are there other spin-offs? Are there any negative effects? What effect does the DHI have on the wider environment, and what effect does the environment have on the DHI?)

References

Al-Janabi H, Flynn T, Coast J. Development of a self-report measure of capability wellbeing for adults: the ICECAP-A. *Quality of Life Research* 2012; 21:167-176.

Chalabi Z, Lorenz T. 2013. Using agent-based models to inform evaluation of complex interventions. Examples from the built environment. *Prev. Med* 2013; 57:434–35.

Christakis A, Fowler JH. The spread of obesity in a large social network over 32 Years. *N Engl J Med* 2007; 357:370-379.

Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew. Developing and evaluating complex interventions: the new MRC Guidance. *BMJ* 2008; 337: a1655.

Ekeland AG, Bowes A, Flottorp S. Effectiveness of telemedicine: a systematic review of reviews. *International Journal of Medical Informatics* 2010;79:736-771.

El-Sayed A, Scarborough P, Seman L, Galea S. Social network analysis and agent-based modelling in social epidemiology. *Epidemiologic Perspectives & Innovations* 2012, 9:1

[Frerichs L](#), [Araz O](#), [Huang T](#). Modeling social transmission dynamics of unhealthy behaviors for evaluating prevention and treatment interventions on childhood obesity. *PLoS One* 2013; 8(12):e82887.

Hawe P, Shiell A, Riley T, Gold L. Methods for exploring implementation variation and local context within a cluster randomised community intervention trial. *JECH* 2004;58:788-93.

Hawe P, Shiell A, Riley T. Theorising interventions as events in systems. *American journal of Community Psychology* 2009; 43:267-276.

[Leroux J](#), [Moore S](#), [Dubé L](#). Beyond the "I" in the obesity epidemic: a review of social relational and network interventions on obesity. *Journal of Obesity* 2013; 348249.

Ling T. Evaluating complex and unfolding interventions in real time. *Evaluation* 2012; 18:79–91

Little P, Stuart B, Francis N, Douglas E, Tonkin-Crine S, Anthierens S, . . . Yardley, L. (2013). Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet*, 2013; 382: 1175-1182.

Little P, Stuart B, Hobbs F, Moore M, Barnett J, Popoola D . . . Yardley L. An internet-delivered handwashing intervention to modify influenza-like illness and respiratory infection transmission (PRIMIT): a primary care randomised trial. *Lancet* 2015 doi: 10.1016/S0140-6736(15)60127-1

Maglio P, Mabry P. Agent-based models and systems science approaches to public health *American Journal of Preventive Medicine*, 2011; 40:384–392

Mistry H. Systematic review of studies of the cost-effectiveness of telemedicine and telecare. Changes in the economic evidence over twenty years. *Journal of Telemedicine and Telecare* 2012;18:1-6.

Mistry H, Garnvwa H, Opong R. Critical appraisal of published systematic reviews assessing the cost-effectiveness of telemedicine studies. *Telemedicine and e-HEALTH* 2014;20:609-618.

Murray E, et al. 2016. Accompanying Paper.

[Pachucki M](#), [Goodman E](#). Social Relationships and Obesity: Benefits of Incorporating a Lifecourse Perspective. *Current Obesity Reports* 2015; 4:217-223.

Petticrew M, Anderson L, Elder R, Grimshaw J, Hopkins D, Hahn R., ... & Welch V. Complex interventions and their implications for systematic reviews: a pragmatic approach. *Journal of Clinical Epidemiology* 2013; 66:1209-1214.

[Powell K](#), [Wilcox J](#), [Clonan A](#), [Bissell P](#), [Preston L](#), [Peacock M](#), [Holdsworth M](#). The role of social networks in the development of overweight and obesity among adults: a scoping review. *BMC Public Health*. 2015; 15(1):996.

Ramsey SD, Willke RJ, Glick H et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force Report. *Value in Health* 2015;18:161-172.

Sanson-Fisher RW, D'Este CA, Carey ML, Noble N, Paul CL. Evaluation of systems oriented public health interventions: alternative research designs. *Annu. Rev. Public Health* 2014; 35:9–27.

Shiell A, Hawe P, Gold L. Complex interventions or complex systems? Implications for health economic evaluation. *BMJ* 2008;336:1281-1283.

Threlfall AG, Meah S, Fischer AJ, Cookson R, Rutter H, Kelly MP. The appraisal of public health interventions: the use of theory. *Journal of Public Health* 2015; 37:166–171.

Yardley L, Morrison L, Bradbury K, & Muller, I. The Person-Based Approach to Intervention Development: Application to Digital Health-Related Behavior Change Interventions. *Journal of Medical Internet Research* 2015; 17:e30. doi: 10.2196/jmir.4055

Yardley L, Ware L, Smith E, Williams S, Bradbury K, Arden-Close EJ, . . . Little P. Randomised controlled feasibility trial of a web-based weight management intervention with nurse support for obese patients in primary care. *Int J Behav Nutr Phys Act* 2014; 11(67): 1-11.

Yardley et al 2016. Accompanying Paper.