Medication Adherence: Improvements via eHealth Behaviour Change Interventions

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**Executive Summary**

Adherence to medication, particularly for chronic illness, has traditionally been poor, occurring only about 50% of the time. Given that the prevalence of chronic illness has never been higher, the potential effects of non-adherence are vast. Non-adherence is thought to be the cause of over 300,000 deaths in Europe and America, while costing over €300 billion, annually. Thus interventions aimed at reducing non-adherence are of critical importance.

From a behavioural perspective, common predictors of non-adherence include procrastination, forgetfulness, side effects, the challenge of managing multiple prescriptions, misunderstanding disease, imperfect drug regimens, cognitive impairments, and a reduced sense of urgency due to asymptomatic conditions. Adherence decreases as the complexity, cost, and duration of the regimen increases.

Technology via eHealth has a potentially significant role in addressing some of these behavioural issues. This White Paper focuses on some eHealth behavioural intervention-types, and provides some recommendations of ways to develop such interventions.

In terms of the active ingredients which can be put within technology-enabled interventions Feedback, and Reminder-systems are two of the more popular and effective behaviour change approaches. However, general consensus suggests that the most effective interventions for medication non-adherence are complex, including combinations of more convenient care, information, counselling, reminders, self-monitoring, reinforcement, family therapy, and other forms of additional supervision or attention.

A number of high-level, general recommendations from this report are that: 1) Stakeholders need to ensure that there is clarity about the facet of adherence upon which they are intervening; 2) Stakeholders need to undertake rigorous due diligence to ascertain answers to a range of questions relevant to the implementation of an effective intervention, including: What intervention? What are the behaviour change techniques (BCTs)/active ingredients? When? (i.e., dosage schedule of the behavioural intervention) By whom? To whom should it be delivered? Through what medium? Where is the intervention provided? These basic, and seemingly obvious questions are not always systematically understood, hence, perhaps, the number of low effect sizes often identified within behavioural interventions in adherence; 3) Interventions benefit by being theory-driven rather than ad-hoc.

A number of more specific suggestions (financial incentives; naming of interventions) are offered as potential approaches to enhance the efficacy of eHealth interventions.
Medication adherence: Improvements via eHealth behaviour change

Background

People don’t take their medication (nor comply with medical advice) all the time. In fact, it is generally acknowledged to occur less than half the time\(^1\). The reasons for this are complex, with an array of social, personal, clinical, educational, and other factors contributing to sub-optimal behaviour. This is not a new phenomenon; rather it is an ever present problem, especially for patients with a chronic illness. There is also a lack of consensus even in the measurement or defining exactly what is meant by ‘adherence’, which adds to the confusion in the design of interventions aimed at changing this behaviour, and hinders attempts to evaluate methods for enhancing compliance\(^2\,^3\). This report aims to provide an overview of behavioural approaches, through eHealth, aimed at attenuating poor or non-adherence.

Adherence is a broad term, the most frequently cited conceptual definition of which is “the extent to which a person’s behaviour – taking medication, following a diet, executing lifestyle changes – follows medical advice”\(^4\). A condition-level medication possession ratio of below 0.80 is the threshold commonly used by researchers to be (non)adherent, and a ratio of 0.80 or greater to be adherent (i.e., taking 4/5 pills)\(^5\,^6\). However, in essence it boils down to: are you taking your medications, and are you taking them properly?

Much of the research\(^7\) has focused on chronic care adherence (e.g., cardiovascular disease; human immunodeficiency virus, diabetes; asthma/chronic obstructive pulmonary disease, etc.). In 2003 the World

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\(^6\) Coarse classification: ‘high adherence’ (≥80%), ‘intermediate adherence’ (40–80%), and ‘poor adherence’ (<40%)

\(^7\) A majority of which, in particular in relation to cost issues, relates to a US context.
Health Organisation (WHO) published (and since regularly updated) a document relating to a review of adherence across long-term (LT) chronic conditions (incl. Asthma; Depression; Diabetes; Hypertension)\(^8\,^9\).

A range of recommendations were included in this widely cited report, key among which is that adherence is an important modifier of health system effectiveness, and that increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments (\(p. \text{xiii}\)), and thus health systems must evolve to meet new challenges.

**Non-adherence**

Patients' *non-adherence* (i.e., the absence of the optimal behaviour [the adhering]), is a very large problem. While many studies, often with industry input\(^10\), suggest that 75% of patients do not take their medication as prescribed, and others suggest non-adherence may run at about 20-25\%\(^11\), consensus suggests that nonadherence runs at approximately 50\% (with a range of 0-100\%\(^12,13\)). The potential costs of non-adherence in this context is therefore a major concern\(^14\). As approximately 91\% of (US) adults aged between 57-85 years take at least one prescription drug a day, and 29\% take five or more medications on a regular basis, the potential effects of non-adherence are vast.

Non-adherence is estimated in America to lead to US$47 billion in drug-related hospitalisations each year\(^15\), and is therefore, appropriately, considered America’s ‘other’ drug problem. It is of course a global trend, and the clinical and economic costs in Ireland, and Europe are similarly vast\(^16\); essentially we pay a catastrophically high price for the absence of optimal adhering. It has been found that even


\(^10\) E.g., National Council on Patient Information and Education (NCPIE); Express Scripts.


\(^12\) McDonald, H. P., Garg, A. X., & Haynes, R. B. (2002). Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA*, 288(22), 2868-2879.


\(^15\) National Council on Patient Information and Education (NCPIE);

initial prescriptions go un-filled, thus ensuring that no adherence can take place. In one study\(^\text{17}\) in which 423,616 e-prescriptions for new medications were identified (3634 prescribers/280,081 patients), 24% of e-prescriptions for new medications were never even filled. Similarly, a recent systematic review of five prior systematic reviews found 771 individual factor items were identified as relating to non-adherence, of which most were determinants of implementation (initial use), and only 47 determinants of persistence with medication (continued/adherent use)\(^\text{18}\). This behaviour thus ensures little potential for health outcome improvements, as the full benefit of many effective medications will be achieved only if patients adhere to prescribed treatment regimens\(^\text{19}\) (assuming an optimal medication regime\(^\text{20}\))

**Clinical costs of non-adherence**

The exact relationship between non-adherence and improved health outcomes is uncharted, a challenge being that there are a lack of consistent data and of well-designed trials\(^\text{21}\). However, in general findings are that poor/non-adherence is related to negative outcomes. In a recent meta-analysis (\(K = 21\); \(N = 46,847\))\(^\text{22}\), good adherence - compared with poor adherence - was associated with lower mortality (odds ratio 0.56\(^\text{23}\)).

The Medication Adherence Clinical Reference, from the American College of Preventative Medicine, report that nonadherence accounts for 10% to 25% of hospital and nursing home admissions, and that recent research has found medication nonadherence to result in: 5.4 times increased risk of hospitalisation, rehospitalisation, or premature death for patients with high blood pressure; 2.5 times increased risk of hospitalisation for patients with diabetes; and more


\(^\text{20}\) For an alternative view on this, see p.26


\(^\text{23}\) 56% improvement with adherence (or 56% worse with non-adherence)
than 40% of overall nursing home admissions\textsuperscript{24}. Non-adherence is thought to result in the mortality of 125,000 patients in the US and 200,000 patients in the EU\textsuperscript{25,26}.

In general, and as stated in the 2003 WHO report, poor adherence to treatment of chronic diseases is a worldwide problem of striking magnitude, with the impact growing as the burden of chronic disease grows worldwide, the consequences being poor health outcomes and increased healthcare costs.

**Economic costs of non-adherence (The costliest health condition)**

The New England Healthcare Institute (NEHI) estimates that nonadherence along with suboptimal prescribing, drug administration, and diagnosis could result in as much as $290 billion per year in avoidable medical spending or 13% of total health care expenditures\textsuperscript{27}. Annually in the US, non-adherence costs $2,000 per patient in physician visits, and critically the rate of non-adherence is expected to increase as the burden of chronic disease increases\textsuperscript{28}. In Europe the figures are equally staggering, with non-adherence estimated to cost in the region of €125 billion annually\textsuperscript{29}.

For example, a 2005 study\textsuperscript{30} ($N = 137,277$ chronic condition patients [diabetes, hypertension, hypercholesterolemia, and congestive heart failure] under age 65) found that a high level of medication adherence was associated with lower disease-related medical cost (diabetes and hypercholesterolemia) and critically, higher medication costs were more than offset by medical cost reductions, producing a net reduction in overall healthcare costs.

For diabetes, hypercholesterolemia, and hypertension, cost offsets were observed for all-cause medical costs at high levels of medication adherence, while for all four of the conditions, hospitalisation rates were significantly lower for patients with high medication adherence.


\textsuperscript{27} [http://www.nehi.net/bendthecurve/sup/documents/Medication_Adherence_Brief.pdf](http://www.nehi.net/bendthecurve/sup/documents/Medication_Adherence_Brief.pdf)


\textsuperscript{29} European Alliance for Personalised Medicine: [http://www.euapm.eu/articles,1,66.html](http://www.euapm.eu/articles,1,66.html)

In concordance with impact on direct healthcare costs (hospitalisations), Express Scripts, the largest pharmacy benefit management (PBM) organisation in the US, seeing 1.4 billion prescriptions a year, report that the US wasted $317.4 billion in 2013 treating unnecessary medical complications that could have been avoided if patients had taken their medications as prescribed. This represents more money than the US spent treating diabetes, heart disease and cancer, combined.

**Predictors of non-adherence:**

As stated, non-adherence represents a complex interplay of issues, and a vast number of variables are consistently identified as predictors of non-adherence (or of adherence). There is general consensus\(^\text{31}\) that these variables sit within one of five wider factors:

1. socio-economic
2. therapy-related
3. patient-related
4. condition-related
5. health-system/HCT related factor (Figure 2)

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\(^{31}\) Sabate, E. Adherence to long-term therapies: Evidence for action. Geneva, Switzerland: World Health Organization; 2003: *Adherence is simultaneously influenced by several factors*
From a patient (behavioural) perspective, common predictors of non-adherence include procrastination, forgetfulness, side effects, the challenge of managing multiple prescriptions, misunderstanding disease, forgetfulness, imperfect drug regimens, cognitive impairments, and a reduced sense of urgency due to asymptomatic conditions, adherence decreases as the complexity, cost, and duration of the regimen increases\textsuperscript{32}. Some detail on key predictors are outlined below:

- **Purposeful**
  - In one recent study, with an analytic sample of 24,017 adults - with a range of chronic conditions including asthma, hypertension, diabetes, and depression - unintentional non-adherence was not random and was in fact predicted by medication beliefs, chronic disease, and sociodemographic\textsuperscript{33}

- **Money**
  - In another study\textsuperscript{34}, adherence was lower, primarily based on two socioeconomic factors (Non-formulary status of medications [i.e., generic, and not covered under insurance: odds

\textsuperscript{32} Most sources address these findings. Some examples: FICO; NEHI; Sabate, 2003 (WHO); McDonald et al., 2002
ratio [OR] 1.31 compared with preferred medications; residence in a low-income ZIP code [OR 1.23 compared with high-income ZIP code]).

- FICO\textsuperscript{35} suggest that among the factors that influence medication adherence risk are job and home stability. People who have been in a job or home for only a short period of time are at higher risk of not taking their medications correctly. Even those who don’t own a car are at higher risk than those who do.

- Demographics

  - Age also influences this behaviour\textsuperscript{36}, and some stakeholders (e.g., FICO) argue that young adults, particularly college students, are at high risk of not following doctor’s orders, as are people over the age of 80.
  
  - Gender can play a part, with for example some research suggesting that men are less adherent if the prescribing doctor is a woman (Figure 3).

- Cognitive biases (e.g., supposed ‘irrationality’)

  - People often make health-related decisions based upon probabilistic assessment bias. They tend to overestimate the probability of unlikely events (such as winning the lottery) and underestimate the probability of likely events, such as being diagnosed with diabetes if they are obese\textsuperscript{37}. A range of other cognitive/attitudinal forces also play a part (e.g., illness perceptions, benefit beliefs, etc.)

It is not only the patient who matters in reducing non-adherence. Clinicians, including pharmacists, are critical both in creating a supportive ecosystem for patients, and in how they themselves interact with potential interventions. For example, there is an acknowledged lack of use of evidence-based approaches by clinicians\textsuperscript{38}, also identified in a recent ARCH systematic review\textsuperscript{39} – which can impact on patient health outcomes.

Express Scripts - who see 1.4 billion prescriptions a year - run predictive models using more than 300 variables, many of which reveal actionable information to battle non-adherence. Thus it should at this

\textsuperscript{35} US software company who provide the Medication Adherence Score


\textsuperscript{37} See the work of renowned financial psychologists/behavioral economists e.g., Daniel Ariely/Daniel Kahneman


point be glaringly obvious that adherence/non-adherence is an inherently complex issue. The complexity can be illustrated within diabetes, which alone could involve a treatment regimen including:
- special diet,
- smoking cessation,
- oral hypoglycaemic drugs,
- and risk management, usually involving additional drugs\(^40\).

It should therefore also be obvious that other than complex solutions may be unlikely to result in anything other than limited, short-term, or even negative consequences (\textit{A more complete list of the specific predictors, per factor, is provided in Appendix B})

**How to reduce non-adherence**

As stated, it is acknowledged that increasing the effectiveness of non-adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments.

The primary responsibility for reducing non-adherence appears to have fallen upon the behavioural sciences; psychology, and to a lesser degree economics (financial psychology/behavioural economics\(^{41,42}\)). This is not to suggest that only behavioural interventions can, or ought to play the only role (see Appendix A). Overly focusing upon the responsibility of the patient may contribute to the relatively low effect sizes seen in non-adherence research\(^43\). For example, some of the key economic and social concerns which need to be addressed in relation to adherence include access to health care and medicines, limited literacy, and provision of effective social support networks\(^44\). A recommendation from the WHO is that a multidisciplinary approach towards adherence is needed, and requires coordinated action from health professionals, researchers, health planners and policy-makers, which, in turn is likely to enhance outcomes.

Notwithstanding these caveats, the focus of this report relates to behavioural mechanisms. Axiomatically, adherence to long-term medication regimens requires behavioural change, which involves learning, adopting and sustaining a medication-taking behaviour, strategies such as providing rewards, reminders


\(^{42}\) Express Scripts suggest that 69% of treatment non-adherence are related to behavioural factors (see Figure 3)


\(^{44}\) Sabate, E. (2003).
and family support to reinforce the new behaviour have been found to improve adherence in chronic illnesses\textsuperscript{45}. eHealth interventions that incorporate behavioural methods (e.g., self-monitoring, goal setting, immediate feedback, contingency management) produce larger effect sizes for health behaviours and their associated outcomes than interventions that rely solely on education\textsuperscript{46}. Figure 3 outlines some predictors and potential interventions for non-adherence.

\textbf{Figure 3:} Infograph of predictors and interventions for non-adherence. (Express Scripts)

\textsuperscript{45} Some of these reviews aggregated within Sabate, E. (2003). For more of these reviews see Appendix B.

A meta-analysis from 2003\textsuperscript{47} found that interventions (behavioural; educational; combined) improve adherence by 4-11%. The overall effect sizes for behavioural interventions was 7%, for educational interventions it was 11%, while for combined interventions was 8%. When stratifying the combined intervention group by type of behavioural intervention, mail reminders had the largest impact (4%). While no single strategy dominated, highest confidence was attached to the ES identified through the behavioural interventions (7%) as they were a statistically homogenous group.

In spite of the promise of behavioural interventions it is acknowledged that no single intervention targeting patient behaviour is effective\textsuperscript{48}, and the most promising methods of improving adherence behaviour use a combination of strategies, including: patient education; behavioural skills, self-rewards, social support, telephone follow-up.

**The role of technology?**

Many key stakeholders, who may benefit from, and could facilitate better adherence (insurance companies, HCOs, pharmacists), do not have - or perhaps are not prepared to expend – the resources needed to undertake the level of personal follow-up (or build in layer of evidence/theory-supported complexity into an intervention), which may be necessary for successful implementation.

Thus technology via eHealth has a potentially significant role, albeit as a workaround to a genuinely sustainable model. For the sake of this report, eHealth\textsuperscript{49} is used as a proxy for learnings from telehealth, telemedicine, essentially connected health; a liberal reading therefore of some of the relevant literature.

One critical advantage of eHealth interventions is that they are usually (inter)active systems, rather than passive which can report more modest improvements over the long-term\textsuperscript{50,51} (e.g., a calendar on the packages which do not, as part of their design, actively interact with the patient). eHealth interventions also can be readily scaled (ease; expense) to meet the demands of large numbers of patients. Thus if


\textsuperscript{49} A study in 2005 found 51 unique definitions for the term eHealth, with some arguing that it is interchangeable with health informatics with a broad definition covering electronic/digital processes in health, while others use it in the narrower sense of healthcare practice using the Internet, while others include applications on mobile phones (mHealth)\textsuperscript{49}


reminders are deemed as an approach, then integration into everyday products (e.g., smartphone technology) would facilitate implementation on a potentially vast level.

Finally, eHealth/active systems tend also to be personalised/tailored, in that they are guided\textsuperscript{52} by the patient actually \textit{doing} something, creating a behavioural feedback loop, which we know from behaviour-change research to be one of the most consistently effective in terms of attenuating target behaviours\textsuperscript{53}.

**Types of behaviour change interventions**

A 2014 report of adherence in Ireland, suggested that the intervention tools most commonly employed, which improved adherence included: improving patient education about the disease/treatment through digital means (e-channels), patient literature or simple discussions with the patient; monitoring patient adherence; using reminders; simplifying medication regimens or employing more convenient care methods\textsuperscript{54}.

There are a range of these tools (aka behaviour change techniques [BCT]/\textit{active ingredients}\textsuperscript{55}) which can be used in behaviour-change interventions (electronic or otherwise), and a recently developed taxonomy of Health IT (eHealth) for medication adherence\textsuperscript{56} identified 16 main types of offerings as outlined in Table 1 below:

\textsuperscript{52} Although not always: reminder systems, while providing feedback, are not necessarily based upon the absence/presence of a patient’s behaviour (i.e., an automatic reminder system may be used: see Note to Table, page 14).


<table>
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<th>Health IT offerings</th>
<th>Interaction</th>
<th>Health information storage</th>
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<th>Multiplicity</th>
<th>Human involvement</th>
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**Legend of abbreviations:**

- **A**=Active interaction: Users are actively involved in data input (e.g., selection of medications during the ordering process);
- **P**=Passive interaction: Users are not continuously involved in data input (e.g., home monitoring must be initially set up but there is no continuous need for interaction);
- **S**=Storage of health information: Users’ information are stored by the health IT offering;
- **NS**=No storage of health information: Users’ information are not stored by the health IT offering;
- **M**=Mobile usage: The health IT offering can be used everywhere;
- **S**=Stationary usage: The health IT offering is bound to a specific environment;
- **I**=Individual experience: The health IT offering is used by a single user;
- **G**=Group experience: Functionality of the health IT offering leverages interaction of multiple users;
- **H**=Human involvement: Service provision requires input from medical professionals or other experts;
- **NI**=No human involvement: Users do not depend on input from medical professionals or other experts;
- **F**=Feedback: The health IT offering provides health-related feedback to the user (e.g., feedback by other users or experts in online support communities on health-related topics);
- **NF**=No feedback: The health IT offering does not provide health-related feedback to the user (e.g., no health-related feedback while locating a pharmacy);
- **P**=Personalization: Users can tailor the health IT offering to their needs and preferences;
- **G**=Generalization: Users cannot tailor the health IT offering to their needs and preferences;
- **P**=Health IT added in the first iteration;
- **P**=Health IT added in the second iteration;
- **P**=Health IT added in the fourth iteration.
Of these, several approaches are consistently identified in the literature as effective:

**Feedback**

A popular active ingredient, and arguably one of the most effective behaviour change technique is feedback (or feedback systems; feedback loops etc.). In conjunction with interventions which prompt self-monitoring (e.g., daily diaries, etc.), feedback (information, cognition, emotion, social support, physiological), represent one of the two more consistently effective ways to change behaviours, for example in increasing healthy behaviours, such as better diet, exercising more frequently, drinking less, and stopping smoking\(^{57}\). While important as a key base within behaviour-change interventions in general, feedback regarding adherence to medication is an important behavioural clinical strategy\(^{58}\), and it could be further argued that a majority of the intervention types in this area, whether eHealth enabled or otherwise, to some degree represent a version of feedback.

**Reminders**

Reminder systems - related to (or nested within) feedback - are another popular intervention type in the adherence literature. It could be argued that we have disappeared down a rabbit-hole looking for the perfect reminder intervention, which may be blinding researchers/stakeholders to other types of equally non-complex intervention modalities, seldom, unfortunately, developing at examples of intelligent reminding\(^{59}\) which may account some of the small effect sizes.

This is not to suggest that reminder systems, via technology, are not useful. However, results from a study in 2015\(^{60}\) (including asthma, coronary heart disease, diabetes mellitus, hypertension) are emblematic of the area: “results showed mixed evidence regarding the benefits of interventions because of the variety of the study designs and the results found. Nevertheless, the interventions do seem to have been beneficial, as 65% of the studies had positive outcomes”.

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58. Feedback which we will address alone, is a key health behavioural strategy and one most recommended in this report.


Reminders come in a variety of flavours. The big favourite has traditionally been the Short Message Service (SMS) reminder (a simple textually-based, brief message: “It is 12.00. Take X medication”, etc.). There are also more creative approaches, such as audio-visual reminders (visual cuing), electronic reminder devices; pager messages. Furthermore, reminders can work for a range of adherence-related behaviours (medication compliance, healthy lifestyle, clinic attendance, etc.).

Examples of these types of interventions are:

- Cues linked to activities, such as meals or bedtime (Figure 4)
- Interactive voice response tele-monitoring interventions have been shown to improve adherence to medications
- Electronic reminders have improved prescription refill and adherence to dosing schedules; computerized alerts to care providers in the outpatient setting have improved medication reconciliation rates and safety-related processes of care
- An automatic alert to pharmacists about potentially inappropriate medications (e.g., amitriptyline and diazepam) for elderly patients led to significant decreases in the dispensing of these medications
- An automated alert to care providers increased the ordering of laboratory tests to monitor for potential adverse drug effects
- Industry-based efforts to improve timing of reminders and reinforcement-type cues have been introduced and tested in the form of calendar-based blister packaging.
- Especially when used in combination with education and other reminder strategies, the calendar-based blister packs have been shown to improve medication adherence, although attention has refocused to relatively simple approaches, such as “reminder” packaging, that can be widely implemented for once-daily medications take for chronic diseases.

**Complex interventions (vs. simple)**

There is consensus, perhaps due to the fact that poor/non-adherence involves an interplay of different factors, that outcomes from complex interventions (i.e., number of moving, discrete parts) are better supported by empirical evidence.

A review in 2002, of Interventions to enhance patient adherence to medication prescription, found that “almost all the interventions that were effective for long-term care were complex, including combinations of more convenient care, information, counselling, reminders, self-monitoring, reinforcement, family therapy, and other forms of additional supervision or attention”63

Complex interventions, may simply represent inclusion of multiple steps or phases or BCTs. As the previous example, perhaps an eHealth feedback system, providing monitoring of pills, to which could be added data-gathering from a Wireless body sensor network, topped off with a weekly phone call from the pharmacist.

It is important to note that *complex* does not axiomatically signify good, nor does less complex signify poor, and this is an important distinction in relation to applied research. A less complex/simple intervention may in fact be optimal, depending on: research question, outcome desired, resources available. A study/project implementing a less complex intervention may, or may not, have an equally valid theoretical/evidential underpinning as a complex intervention (i.e., both involve an understanding of why something being done, and what outcome expected, etc.). However, due to study or stakeholder resources, a less complex, and thus often less expensive version of an intervention may be implemented.

- For example, instead of a feedback plus face-to-face therapy intervention, stakeholders may implement only an eHealth feedback component, which have been shown to have consistent effect sizes. Feedback loops are a powerful behaviour changed mechanism.

Notwithstanding these caveats, there is considerable support for multi-phased/component interventions, and in fact it may be that the inclusion of the human factor (e.g., a pharmacist, in the case of medication adherence) is critical64. Recently an interesting new model, “supportive

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63 McDonald, H. P., Garg, A. X., & Haynes, R. B. (2002). Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA*, 288(22), 2868-2879. (Quote taken from p.2877)

accountability” (wherein patients can call upon active support from relevant individuals, for example a pharmacist) has been articulated as a way for the human factor to complement any eHealth strategy65.

General recommendations

A number of high-level, general recommendations from the 2003 WHO Report, of relevance to stakeholders were that: 1) Patients need to be supported, not blamed; 2) Patient-tailored interventions are required; 3) Health professionals need to be trained in adherence; and 4) A multidisciplinary approach towards adherence is needed.

These are useful in the development of interventions. However, stakeholders interested in increasing adherence/decreasing non-adherence obviously need to understand their own needs initially; namely, is adherence even a key issue for them? If it makes sense to address the issue, then matters of resource expenditure arise: is a company willing to undertake due diligence, ensuring the best likelihood of a successful outcome, or are they willing to accept a lesser outcome (or are they simply constrained)? Regardless of these considerations, and whether a choice of generic/simple interventions versus more complex interventions arise, a number of steps ought to be undertaken.

Step 1: What is adherence?

The first questions to be answered is simply: Is adherence really upon what we are intervening? This relates to the utter complexity even in understanding what adherence/non-adherence is. A recently developed taxonomy66 proposes that ‘adherence to medications’, the process by which patients take their medication as prescribed, can be divided into three quantifiable phases: ‘Initiation’, ‘Implementation’ and ‘Discontinuation’. Thus without knowing upon which phase(s) of adherence a project aims to intervene, valid results/outcomes are less likely.

Step 2: Due diligence

Whether or not a stakeholder endeavours to implement a complex intervention or not, best-practice in behavioural interventions begins with the undertaking of a systematic literature review which is aimed at answering a specific, and granularly pre-specified research question. At a minimum, stakeholders need to review the relevant, extant literature. This – again, at a minimum – allows a stakeholder to be

prepared in their intervention, even if it is a low-level version thereof. Once agreement is made upon what the project hopes to intervene, by undertaking a rigorous preparatory approach, then we must look at some other questions:

1. **What intervention?**
   - What are the behaviours change techniques (BCTs)/**active ingredients**? (i.e., feedback, reminders, etc.)

2. **When?** (i.e., dosage schedule of the behavioural intervention)
   - This is the important matter of **reinforcement scheduling**, which essentially is: when and how often (if at all) is it most effective to provide the stimulus needed to increase the likelihood of a target behaviour (or to reduce the likelihood)?
   - Reinforcement - feedback based on behaviour - is an essential component of all behavioural strategies\(^{67}\). This does not need to be some unnecessarily sophisticated approach. Specifically, research suggests that, again, human interaction, for example in the form of a clinician’s time and attention - or from those people who are most significant to them and most readily available at the time the health behaviour occurs - may be the most powerful available reinforcer\(^{68}\). The key, in the context of eHealth and healthcare resource constraints is how to replicate this **most powerful** predictor.
   - A random schedule can be effective as a way to **maintain** behaviour, hence its adoption by the casino trade among others (e.g., applied behaviour analysis). Similarly, evidence within behavioural economics (arguably a more appropriate term would be Financial Psychology), has identified that a lottery-based (again, random) reward mechanism/schedule is best for optimising and maintaining a target behaviour.

3. **By whom?**
   - By whom will any human-component – if being utilised – be most effectively provided: Pharmacist vs nurse vs carer, or is it irrelevant?
   - Even if the intervention is less complex (i.e., no human-component) whom does the patient even trust sufficiently to be the provider/driver of a technological solution?
   - To **whom** should it be delivered? Patient, carer, etc.

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\(^{67}\) Sabate, E. (2003). Adherence to long-term therapies: Evidence for action. Geneva, Switzerland: World Health Organization. (Report has been regularly updated since 2003). For more of these reviews see Appendix A

\(^{68}\) Ibid.
4. Through what medium?
   - Telephone call; smartphone app; SMS, sensor-technology, etc.
   - Again, the issue of Trust arises, in that: will patients believe in the efficacy, safety, and security of the technology-based intervention?\(^{69}\)

5. Where is the intervention provided?
   a. Context is critical\(^{70}\): Online/always-on (or Pharmacy or GP or Hospital or postal/home)

By asking these, and other relevant questions - will I be satisfied with a (potential) 5% effect size from a simple intervention, versus a (potential) 10% from a complex intervention? What clinical benefit is accrued by reducing this non-adherence? What is the cost-benefit or cost-utility? - stakeholders give themselves the most likely chance of a successful implementation, and effective, or at least evaluable, outcomes.

**Step 3: Build the intervention using theory**

Whether simple/generic or more complex, interventions benefit by being theory-driven rather than ad-hoc, and in fact the Medical Research Council’s (UK) widely used framework for the development of complex interventions, highlights the importance of a theoretical understanding of the likely process of behaviour change by drawing on existing evidence and theory\(^{71,72}\)

Leventhal and Cameron\(^{73}\) outline five general theoretical perspectives on adherence: 1) biomedical perspective; 2) behavioural perspective; 3) communication perspective; 4) cognitive perspective; and 5) self-regulatory perspective. A number of well-established behavioural theories, particularly the Trans-Theoretical (Stages of Change) Model provide valuable insight into non-adherence, which relate to the taxonomy mentioned previously (see Footnote 50). Alternatively, behaviour learning theory is used as a foundation for many reminder interventions\(^{74}\).

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Theory provides a helpful basis for designing interventions to change behaviour but little guidance is offered on how to do this. However, the recent development of an extensive list of behaviour change techniques (with definitions) and ways in which to link techniques to theoretical constructs (COM-B model; the Behaviour Change Wheel)\(^7\) are proving useful and practical insights into how effective and evidence-based behavioural eHealth interventions can be developed and deployed.

**Step 4a: Complex or not?**

At this point, the decision in relation to whether there is the need for a complex intervention, or a simpler one, is likely to have emerged (i.e., preparatory research will outline what is needed). Therefore, this paper will not labour the point in relation to the choice of intervention (i.e., complex or otherwise), and some of the BCTs discussed previously which could reasonably be used within an eHealth intervention (feedback, reminders, etc.) should suffice. However, briefly discussed will be the need or not of a tailored/personalised approach.

**Step 4b: Personalised or not?**

Personalised (tailored) medicine, facilitated by big data, is now ‘accepted’ uniformly as positive. This paradigm promulgates the Virtual Physiological Human framework, a core target of the 7th Framework Programme of the European Commission, to support the development of patient-specific computer models and their application in personalised and predictive healthcare.

However, what is often glossed over, is that due to the complexity and multiple determinants of non-adherence, the prediction of non-adherence of **individual** patients is an exceedingly difficult matter\(^7\), and thus commensurately, attempts to intervene also face this challenge.

Tailoring, in spite of the potential upsides, in addition to the inherent complexity, carries attendant resource costs, as there is the obvious need to address (in the absence of available big-data predictive models): the condition; the population; the provider; the setting; the culture; the type of drug/clinical intervention, etcetera.


Relatedly, many key stakeholders in the health ecosystem, including the WHO, are beginning to focus on commonalities among conditions, and thus interventions aimed at reducing one may have an impact on reducing others. More specifically, interventions aimed at reducing behavioural risk factors in one condition are likely to generalise to their conditions. A broad consensus among health stakeholders in Ireland (e.g., HSE, Alzheimer’s Society of Ireland, The Irish Cancer Society, Diabetes Ireland, The Irish Heart Foundation) and Internationally (WHO, CDC, NHS) has emerged in terms of developing general population health through facilitating individuals with reducing modifiable risk factors. A number of risk factors are common to many of the leading chronic diseases whereby they are often associated with two or more conditions (Department of Health, 2014). Further, each chronic disease can also be associated with two or more risk factors (ibid).

Thus, generic approach to personalised care, while counterintuitive, may be optimal. For example, non-adherence was reduced when e-prescriptions were transmitted directly to the pharmacy, rather than printed to give to patients (OR = 0.54)77. In Sweden, for example, all drug prescribing is done electronically (a message is sent directly from the doctor’s office to the pharmacy), which cuts down on medical errors, and is thought to save 1-2 hours of work by the pharmacists per day; generic (all patients equal) approaches, unenhanced by any personalisation78.

Thus in this era of marketing/push for tailored and personalised medicine – and the range of reports and evidence which highlights their advantages - it can be useful to remember that there are certain generic, emotional drivers of behaviour (fear, sadness, anger, etc.). And it can be argued that within the domain of healthcare it may be more valuable to look at seemingly ‘irrational’ behaviours as the best guide to predicting behaviours, such as adherence, wherein feelings can outweigh facts79,80.

Again, it is important to undertake the aforementioned preparatory steps, one of which may also relate to identifying (for a condition) exactly what level of personalisation/tailoring is necessary or appropriate, which may also assist in the process of developing an adherence-intervention to which the patient will...

78 ‘Mass customisation’ is a technology improvement-related factor likely to override some of these caveats.
actually adhere, which is another problem in the area, wherein again only about half participant/patients tend to adhere to eHealth interventions\(^81\).

**Additional recommendation I: Use of names**

There is a reason technology companies name their utility bots (Siri; Cortana; ELIZA [the original computer therapy bot]); **so that we can ‘connect’ with them.** We connect with other people, even if that other person is nothing more than an algorithm with a friendly name (or voice). It is possible that this – our inherent need for connection - is the reason why complex interventions (number of moving parts, often with human interactional components) tend to provide the largest effect sizes.

This is, on reflection, rather obvious. After all, during ill-health – particularly chronic ill-health – we are in a period of utmost vulnerability. And it is during these times that a hand on the shoulder is needed. Females, primarily, are known to produce the stress hormone oxytocin – which has the effect of reducing cortisol - when in the presence of other women and children, which has a direct positive impact on health\(^82\). Thus the notion that we need connectedness, and that it may have both direct and indirect health effects, is not unreasonable.

However, while technology can enhance the *quantity* of connectedness, it may not be in a position to optimise the quality, which is where human contact plays a significant, if not in fact necessary part\(^83\).

And this is not just in the field of adherence, but right across the spectrum of health and social/behavioural-related interventions. The salient point being that putting another human into the mix improves outcomes. This general area can be argued to relate to ‘Trust’, which may be the key, albeit seldom spoken of ingredient in the use/adoption of connected health technologies. A recent ARCH systematic review on the barriers to clinician use of connected health-type solutions\(^84\), reported

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\(^83\) Mohr, D., Cuijpers, P., & Lehman, K. (2011). Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. *Journal of Medical Internet Research*, 13(1), e30

that Trust – in the information contained in the solutions; in the provider of the solution – is one of the critical predictors of effective implementation; credibility of eHealth (by patients) is no different\textsuperscript{85}

Thus, in advance of a more complex intervention, which can often include a human/connective element, perhaps the addition of a name to the technology intervention (“Adherey, your adherence buddy”) may improve behaviour.

**Additional recommendation II: Financial incentives**

A recommendation is made for the use of a monetary reward mechanism, which could be a potentially effective way to modify poor adherence. While this may not fit the mould of an eHealth intervention\textsuperscript{86}, money (in the guise of socio-economic circumstances) is often a significant driver in behaviour change, and an oft-mentioned as a key predictor of non-adherence\textsuperscript{87}.

Monetary rewards are not a crazy thought, given the varied role which finances play in adherence, whether it be via healthcare funding or a patient’s ability to access medication, to providing an incentive to the patient based on adherence. In one study, which outlined the high frequency of patients not even filling their first prescriptions, the authors recommended interventions to address economic barriers and increase electronic integration\textsuperscript{88}. Also, it has been recommended that healthcare systems consider pay-for-performance techniques to provide an incentive to all stake-holders to work harder to track and improve adherence for important chronic clinical conditions\textsuperscript{89}. Further, studies providing discounts/vouchers, employing “payment by results” initiative\textsuperscript{90}, co-payments and improved prescription drug coverage, have been shown to be effective\textsuperscript{91}.

However, it depends how this considerable force is wielded, and whether monetary forces marshal or overwhelm a patient’s intrinsic motivation. For example, if an individual believes possessing good health is a positive attribute, and they desire to have this/it fits their identity, then they may undertake the necessary steps to achieve this, including remaining adherent to a medical regimen. However, if for a


\textsuperscript{86} Although the mechanism for incorporating a financial incentive programme could

\textsuperscript{87} Sabate (2003).


variety of reasons (mental health; self-sabotage; literacy/education deficit, etc.) that particular drive is lacking, a monetary reward may be effective.

**Non-adherence: Always bad?**

Before completing this paper, it is important to highlight an issue not given sufficient consideration in this area; namely, that not all non-adherence is negative, nor all adherence positive.

As stated earlier (p.6) a key predictor for non-adherence is *purposeful/intentional* non-use (patients choose not to comply with their medication). On the face of it this seems like an issue to be intervened upon. However there are times when non-adherence should be commended, and some rational reasons exist why non-adherence may be a good thing from a patient perspective; namely, over prescribing, whether through incompetence or greed (i.e., prescribing behaviours modified due to gifts from industry\(^{92}\)); polypharmacy; patients’ ability to make decisions based on biofeedback (physical symptoms: e.g., non-adherence to depression/anxiety medication due to improvement in symptoms based on alternative, and appropriate modification regimens (reduction of substance use; exercise; diet, etc.).

Good adherence to harmful drug therapy has in fact been shown to be associated with increased mortality, with odds ratio in one study at odds ratio 2.90 (i.e., 290% higher risk than non-adherent).

This factor of intentional non-adherence ought therefore to be given due consideration in the design of any interventions aimed at reducing non-adherence, by asking the question: *is the patient right to avoid it?*

Another issue relates to the area of adherence in general. Traditionally heterogeneous effect sizes are found within discrete interventions, suggesting that the best that can be hoped for via behavioural interventions is to merely scratch the surface. Perhaps 5-15% is as good as it gets.

If that is the case, then the argument for implementing non-complex (and thus usually less expensive) interventions increases, leaving constrained resources to be better spent on alternative research or clinical work. Or even upon lobbying the more strategic stakeholders (government; insurance companies) for more structural changes, which may represent a greater proportion of the missing 85%.

While behavioural interventions are not to be discounted, more global changes may attenuate poor/non-adherence in a more meaningful way, increasing the state’s coffers, not coffins.

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**Conclusion**

Non-adherence to medication/treatment regimens is a common, costly problem. Where there may be disagreement about how best to impact on this behaviour, some consistent findings have emerged; namely low/moderate effects sizes can be achieved via behavioural interventions via technology, including self-monitoring (e.g., use of diaries, logs, calendarized packaging, electronic reminders, triggers, and alerts), positive reinforcement (e.g., digital feedback mechanisms, trending, incentives, and rewards), and accountability partnering (e.g., provider-patient contracting, Web-based support groups\(^93\): for a list of some related adherence interventions see ARCH white paper\(^94\). However, while stakeholders *may* be able to effect some change in adherence/non-adherence by using a simple behaviour change process *via* technology (SMS messaging), it is nonetheless proposed that complex interventions (technology plus human-contact) are both more likely, and at a stronger level, to change adherence behaviours, as *the most effective interventions use a combination of approaches and address these barriers*\(^95\).

The key way to optimise the chance for effective intervention is to undertake solid, bottom-up research with your own key end-users/patients (via robust and well-resourced qualitative research; via granular mapping of care pathways). A focus on a theory-driven intervention, aided or driven by a systematic review of available literature (at a minimum) will steer stakeholders in more accurate direction.

Of course, ad-hoc decisions based on ‘common-sense’ or anecdotal ‘knowledge’ can and are often chosen over a more focused approach. Companies and other stakeholders who choose this approach, can of course benefit, both in the short-term - by forgoing the resource costs of a systematically designed intervention, which is after all, not usually the *key* component to their business - and farther; after all, they do know their users, sometimes. However, optimising the efficacy of interventions, and thus understanding why something worked, for whom, and for how long, does require a more long-term focus.

A recent paper\(^96\) stated that the issue of low-moderate effects from a traditional model of adherence interventions, represent a **call to arms** to those who desire improvements in this area. Stakeholders who take up this call are likely to be rewarded accordingly.

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\(^95\) Bosworth et al., (2011). p. 415

Appendices

Appendix A
The primary systematic reviews/meta analyses used as data gathering sources:


An obvious overlap exists between adherence (and compliance) and patient/treatment (self)management. For the purposes of this report however, we have primarily focused on reviews/research which specifically and explicitly highlighted the adherence aspect, which is nested in the larger frame of treatment management. Further while not all these papers were individually cited, they all framed the general argument/recommendations.

A number of single study papers from acknowledged experts in the area of behavioural interventions and eHealth (e.g., Susan Michie) were also assessed.


### Appendix B

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<thead>
<tr>
<th>1. SOCIAL AND ECONOMIC DIMENSION</th>
<th>4. THERAPY-RELATED DIMENSION</th>
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<tbody>
<tr>
<td>Limited English language proficiency</td>
<td>Complexity of medication regimen (number of daily doses; number of concurrent medications)</td>
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<tr>
<td>Low health literacy</td>
<td>Treatment requires mastery of certain techniques (injections, inhalers)</td>
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<tr>
<td>Lack of family or social support network</td>
<td>Duration of therapy</td>
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<tr>
<td>Unstable living conditions; homelessness</td>
<td>Frequent changes in medication regimen</td>
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<tr>
<td>Burdensome schedule</td>
<td>Lack of immediate benefit of therapy</td>
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<tr>
<td>Limited access to health care facilities</td>
<td>Medications with social stigma attached to use</td>
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<tr>
<td>Lack of health care insurance</td>
<td>Actual or perceived unpleasant side effects</td>
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<tr>
<td>Inability or difficulty accessing pharmacy</td>
<td>Treatment interferes with lifestyle or requires significant behavioral changes</td>
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<td>Medication cost</td>
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<tr>
<td>Cultural and lay beliefs about illness and treatment</td>
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<tr>
<td>Elder abuse</td>
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<th>2. HEALTH CARE SYSTEM DIMENSION</th>
<th>5. PATIENT-RELATED DIMENSION</th>
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<tr>
<td>Provider-patient relationship</td>
<td>Physical Factors</td>
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<tr>
<td>Provider communication skills (contributing to lack of patient knowledge or understanding of the treatment regimen)</td>
<td>Visual impairment</td>
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<td>Disparity between the health beliefs of the health care provider and those of the patient</td>
<td>Hearing impairment</td>
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<td>Lack of positive reinforcement from the health care provider</td>
<td>Cognitive impairment</td>
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<td>Weak capacity of the system to educate patients and provide follow-up</td>
<td>Impaired mobility or dexterity</td>
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<td>Lack of knowledge on adherence and of effective interventions for improving it</td>
<td>Swallowing problems</td>
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<td>Patient information materials written at too high literacy level</td>
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<tr>
<td>Restricted formularies; changing medications covered on formularies</td>
<td>Psychological/Behavioral Factors</td>
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<td>High drug costs, copayments, or both</td>
<td>Knowledge about disease</td>
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<td>Poor access or missed appointments</td>
<td>Perceived risk/susceptibility to disease</td>
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<td>Long wait times</td>
<td>Understanding reason medication is needed</td>
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<td>Lack of continuity of care</td>
<td>Expectations or attitudes toward treatment</td>
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<td></td>
<td>Perceived benefit of treatment</td>
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<td>Confidence in ability to follow treatment regimen</td>
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<td>Motivation</td>
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<td>Fear of possible adverse effects</td>
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<td>Fear of dependence</td>
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<td>Feeling stigmatized by the disease</td>
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<td>Frustration with health care providers</td>
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<td>Psychosocial stress, anxiety, anger</td>
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<th>3. CONDITION-RELATED DIMENSION</th>
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<td>Chronic conditions</td>
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<td>Depression</td>
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<td>Psychotic disorders</td>
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<td>Mental retardation/developmental disability</td>
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