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Medical Adherence Consortium

Encouraging adherence initiatives: aligning individual, commercial, and social value

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Abstract

It is commonly understood that the most expensive medicines are the ones that are not used. Not only does failure to take prescribed medication correctly – or at all - cost up to US$290 billion annually in the US alone, it can have a major detrimental effect on patient health contributing to an estimated 200,000 deaths in Europe every year. Therefore, improving patient adherence should not be a peripheral consideration when managing patient health but a core priority that needs greater attention.

This paper, produced by the CfBI Medical Adherence Consortiuma, sets out to understand why medicines adherence is difficult to achieve and the barriers that limit success and identifies where efforts should be concentrated to improve adherence. In particular, the need to address 'value misalignment' on low cost high volume medicines, where low prices dis-incentivise manufacturer funded adherence programmes, though the cost and impact of non-adherence to the payer is significant because of the high volume. The consortium concludes by making five recommendations to policy makers, payers, healthcare professionals and manufacturers to recognise adherence in the development of policies and new services, to discover new ways of funding adherence, and to use existing funding more effectively.

Definition of medicines adherence

Adherence is the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation. Initiation occurs when the patient takes the first dose of a prescribed medication. Discontinuation occurs when the patient stops taking the prescribed medication, for whatever reason(s). Implementation is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. Persistence is the length of time between initiation and the last dose, which immediately precedes discontinuation.[2]

a The CfBI Medical Adherence Consortium (www.cfbi.com) brings together a wide range of organisations from across Europe, including stakeholders from industry, healthcare professionals, academics and patient groups, who have a common interest in obstacles to the improvement of medication adherence. Of particular focus is the issue that successful adherence initiatives all too often fail to be scaled up due to economic challenges. This paper aims to set out the nature of the economic challenges surrounding medicines adherence projects and suggest ways of overcoming these challenges

Impact of poor medicines adherence

The WHO calls poor medicines adherence "a worldwide problem of striking magnitude" and there are reports of up to 50% of medications for long-term conditions not taken as prescribed [1]. Poor medicines adherence can:

- **Lead to unnecessary expense to the healthcare system**: costs the US healthcare system $100 billion to $290 billion annually [2]

- **Be detrimental to patient health**: 10% of hospitalisations are attributed to the incorrect use of medicines and there are an estimated 200,000 deaths per annum in Europe as a result of non-adherence [3]

Medicines adherence initiatives

Addressing medicines adherence can lead to both improvements in patient health and savings to the healthcare system. In fact, the WHO stated that any intervention to improve medication adherence to existing treatments would have a greater benefit than the development of new drugs for most medical conditions.[2] Benefits may also be seen for other stakeholders, including carers (e.g. reduced anxiety), employers (healthier workforce), pharmacy (increased loyalty), pharmaceutical companies (improved brand) and Governments/insurers etc.

Adherence initiatives may be seen as any initiative that aims to improve adherence directly or as part of a larger activity. Examples include simple reminders (text, phone or app); increased patient 'activation' and 'engagement' through improved self-monitoring of condition and therapy; automated dispensers; enabling the patient's healthcare professional to better understand the required level of adherence leading to a shared approach with the patient (sometimes called concordance); and other still richer approaches to affecting behavioural change. These can be delivered by a variety of organisations including healthcare bodies, patient support consultancies, pharmaceutical companies, pharmacies, healthcare charities, technology providers and many others.

Barriers to adherence initiatives

However, addressing medicines adherence issues is not a simple task as there are many reasons why patients do not take their medicines as directed. Every meaningful initiative to manage medication adherence should work, but only if it is applied to the right person, for the right problem, at the right time. The complexity of the issue therefore precludes simple solutions, and can be viewed as either essential impediments, or structural complexity.

Essential complexity/impediments	Structural complexities/impediments
• **Intentional vs non-intentional**: whether a patient wants to adhere or not • **Behavioural/belief influences**: does the patient believe in the requirement/benefit of the medicine? • **Difficulty of measurement**: differing measures (e.g. patient-reported, direct observation, prescription monitoring, wearable/ingestible devices, electronic	• **Economic complexities**: mismatch between individual, commercial and social value of adherence activities – the commercial reward for improving adherence is not aligned to the social/personal value that improved adherence generates. In addition, the cost of poor adherence and the potential benefits to improvement are

pill box monitoring), no single agreed approach and difficult to have effective control groups • **Importance of therapy 'feedback'**: when patients can see no change to their health they may assume the medicine is not working and feel less urgency to take it	difficult to estimate and differ for each stakeholder involved. • **Regulatory impediments**: medicines adherence activities operate in a highly regulated environment

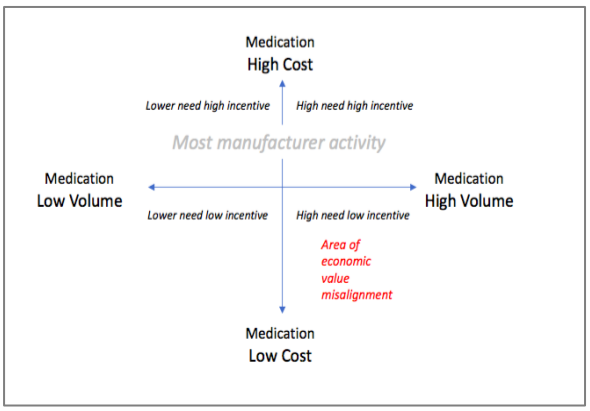
The adherence landscape

Adherence initiatives and patient support programmes are often funded by pharmaceutical companies acting to support individual products (around the pill) or therapies (beyond the pill) services. Indeed, there is often an expectation from payers and providers that pharmaceutical companies should fund the majority of adherence initiatives. However, regulations often restrict the engagement of pharma companies with patients and other stakeholders may have greater influence over patients in their treatment journey.

The consortium argues that there is a significant and vital set of adherence activities that cannot be undertaken, driven, or funded by pharmaceutical companies alone, but should be delivered from within the healthcare eco-system with all parties around the patient playing a part. For example, most patients and their carers interact frequently with pharmacies to have their drugs dispensed and pharmacists are seen as healthcare professionals who are 'therapy experts' by the general public. The consortium believes that pharmacies should take a larger role in adherence management via multichannel interventions. Pharmacists interact in a multi-channel way (face to face or digitally) and are in a position to provide accurate advice to patients. Experience from across Europe shows that pharmacists have been incentivised to take a more active role in the medication management of their patient population (e.g. Medicines Use Review in the UK and the anticoagulant interview in France).

Value misalignment

Although the costs of poor adherence are significant, commercial activity to address this is comparatively small, which could be a sign of economic misalignment (supply not meeting demand) or little demand despite a clear identified need. The consortium feels that there is often a mismatch between individual, commercial, and social value of improving adherence. The economic aspects of adherence initiatives vary greatly, depending on the nature of the condition, the therapy, and other characteristics of the patient and healthcare environment.



There are two key dimensions that describe (at a high level) the economic viability of adherence activities: the unit cost of the medication (high or low) and the total social impact of the condition (see opposite). Total social impact refers to the impact to society as a whole of the condition. This means that rare conditions, while possibly devastating to the individuals suffering with them, are unlikely to have as big a social impact to society as a whole as common conditions. Where the unit cost of the medication is high there is commercial justification for manufacturers to invest in initiatives which will drive sales, where the unit cost is low there is less commercial justification.

When a condition is serious and widespread we can say that it has a large total social impact. When the condition is widespread but less serious (such as a common cold) or is serious but not widespread, then the total social impact of the condition is (comparatively) low. Societal value is very difficult to gauge and goes beyond the cost to the payer. Greater public benefit in adherence would be seen where the societal impact is high but the unit cost of the medication is low and where there is little incentive for manufacturers to invest. This is where there is greatest misalignment of value.

Recommendation 1: The Consortium recommend that policymakers and influencers concentrate on addressing the area of greatest economic value misalignment for adherence initiatives – namely where the volume of prescriptions is high, and cost of drug is low – and focusing on those medications and conditions where non-adherence is considered a significant problem.

Approaches to economic sustainability

The consortium believes that in the case of misalignment of value, payment for adherence improvement initiatives and activities cannot come from pharmaceutical companies alone, but must come from the whole ecosystem including other major beneficiaries of improved adherence. This may include – but is not limited to – the public health system**.**

Recommendation 2: The Consortium recommends that stakeholders identify appropriate and innovative funding mechanisms and take steps to implement these.

Making successful adherence activities truly economically sustainable will require the development of new business models. The consortium believes that whatever the business model, it should be accessible to a broad set of suitable providers of adherence initiatives which could lead to increased innovation from new participants in the market. Funding models should avoid limiting funding by criterion so that only a small number of projects and initiatives are considered for funding. This 'silo solution' approach can act to prevent the emergence of truly inter-disciplinary and innovative approaches.

Recommendation 3: The consortium therefore recommends that any new route for accessing funding to support adherence initiatives be made clear by bodies responsible for setting compensation rules.

Measurement of benefit from adherence initiatives is difficult to derive and requires more work to understand the health outcomes link; however,

Recommendation 4: The Consortium recommends that the burden of proof for adherence activities should be lower than it is for the underlying medication

This is because the level of risk associated with adherence interventions is lower than that associated with the medicines themselves. The payment – and commercial return – for a successful adherence initiative is therefore likely to be aligned to service sector margins rather than to the actual measured benefit of the adherence measure itself.

The role of regulation

It is important to work towards reducing the cost of adherence activities, particularly those flowing from regulatory compliance. These include, regulatory complexity (variance between regions and who is funding the activity); regulatory burden (cost to address regulatory and compliance requirements

seen as a barrier); and regulatory obstruction (direct barrier to some adherence initiatives, e.g. control on patient communication). Maintaining patient safety through effective regulation is vital, but many of these costs are derived from the historic lack of consideration of adherence as a priority.

Recommendation 5: The consortium recommends that regulators, industry, payers, healthcare providers, patient and carer representatives and other stakeholders work together to:

- **Recognise the importance of increasing adherence, and take this into account when drafting regulations;**
- **clearly identify 'best practice' as well as 'minimum requirements' to guide existing and new organisations operating in this market; and**
- **encourage more engagement between the stakeholders in the value chain to work together on standards that meet the regulatory requirements, are usable in practice and reduce the barriers to encourage innovative approaches to be tested and validated.**

Conclusion

The Consortium recognises the widespread commitment and investment of many stakeholders to improve medicines adherence, and in doing so the health and wellbeing of patients. It understands the complex challenges involved but believes the economic case exists to invest in medicines adherence, especially for medicines and therapies that fall into the trap of economic value misalignment. It would encourage all stakeholders to take stock of its recommendations and co-create the solutions that are desperately required.

Recommendations of the Consortium

1. Policymakers and influencers should concentrate on addressing the area of greatest economic value misalignment for adherence initiatives – namely where the volume of prescriptions is high, and cost of drug is low – and focusing on those medications and conditions where non-adherence is considered a significant problem
2. Stakeholders should identify appropriate and innovative funding mechanisms and take steps to implement these
3. Any new route for accessing funding to support adherence initiatives should be made clear by bodies responsible for setting compensation rules
4. The burden of proof for adherence activities should be lower than it is for the underlying medication
5. Regulators, industry, payers, healthcare providers, patient and carer representatives and other stakeholders should work together to recognise the importance of increasing adherence, and take this into account when drafting regulations;
    a. clearly identify 'best practice' as well as 'minimum requirements' to guide existing and new organisations operating in this market; and
    b. encourage more engagement between the stakeholders in the value chain to work together on standards that meet the regulatory requirements, are usable in practice and reduce the barriers to encourage innovative approaches to be tested and validated.

References

1. Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., ... & Matyjaszczyk, M. (2012). A new taxonomy for describing and defining adherence to medications. *British journal of clinical pharmacology*, *73*(5), 691-705.
2. Sabaté, Eduardo. Adherence to long-term therapies: evidence for action. World Health Organization, 2003
3. Rosenbaum, Lisa, and William H. Shrank. "Taking our medicine—improving adherence in the accountability era." New England Journal of Medicine 369.8 (2013): 694-695.
4. Pharmaceutical Group of the European Union "Targeting Adherence - Improving Patient Outcomes in Europe through Community Pharmacists' Intervention" PGEU policy statement on adherence to medicines 2008.

5. Further Information

For further information about this position paper or the CfBI Medical Adherence Consortium please send an email to MA@cfbi.com.

APPENDIX:

Full Consensus Report of the CfBI Medical Adherence consortium

Encouraging Adherence Initiatives: Aligning Individual, Commercial, and Social Value

- The CfBI Medical Adherence consortium has worked for several months to derive a consensus view of the problems surrounding the poor economic sustainability of medicines adherence initiatives.
- This report was collated by the members of the economic sustainability working group of the consortium, based on contributions from consortium members past and present'
- This paper represents the output of this consensus exercise and should be read as an expansion of the arguments presented in the executive summary.

Summary

- The CfBI Medical Adherence consortium is a primarily industrial grouping of organisations who have a shared interest in creating value through improving medication adherence.
- Adherence is an issue that impacts on lives of patients and costs of healthcare delivery. Adherence interventions are characterised as complex and require careful development and implementation. Whilst many interventions have not worked, a small number have delivered measurable sustainable behaviour change, but apart from pockets in TB and HIV where governmental intervention drove implementation, successful pilot programs have not led to scaleable implementation.
- The group has identified economic value misalignment between stakeholders as one key obstacle that has restricted the implementation of adherence improvement activities despite the clear health requirement for them.
- This paper explores the misalignment between individual, commercial and social value that challenges the economic sustainability of adherence initiatives. We advocate that through improved alignment of value between some or all stakeholders increased economic viability of adherence initiatives will result.
- The consortium also considers that the environment for economically sustainable adherence initiatives is more difficult and costly than it need be, resulting in too many initiatives not going beyond pilot phase or failing to move beyond concept.
- Specifically, this paper
    - gives an overview of the shape and complexity of the adherence improvement 'ecosystem'
    - identifies what sort of adherence activity suffers most acutely from value misalignment
    - discusses some characteristics of possible solutions to this economic problem
    - identifies (some) costs that could be safely reduced

- The paper argues that the area where economic sustainability of adherence initiatives is currently lowest and so in the greatest need of addressing is where, for a condition and therapy
    - The social impact of the condition (and hence the impact on non-adherence) is high, and
    - The unit cost of the medication is low.
- The paper argues that in this area there is no obvious economic model and that business model innovation is required to enable sustainable solutions.
- The paper argues that it is important that any adherence intervention can be shown to improve health outcome. However the lower level of risk associated with adherence interventions for medications that have already been proven through the clinical trial process (as opposed to the risk associated with the medications themselves) means that the burden of proof for improved outcomes can be lower than it is for the underlying medication. The usage of a representative sub-population should become the reference as the measurement of the adherence level of an entire population can also be costly.
- The paper discusses the issue of costs – specifically those arising from the regulatory system. And argues that some of the costs described above are accidental and have come about because regulators have historically not considered increasing adherence to be a priority. To this end it recommends that regulators recognise the importance of increasing adherence, and take this into account when drafting regulations.
- This paper advocates a cross industry approach involving all key stakeholders in the wider healthcare sector.

Introduction

Background to the paper

- The CfBI [1] Medical Adherence Consortium brings together a wide range of organisations from across Europe with a common interest in sharing experience, aligning thinking, and jointly identifying and addressing common obstacles to the improvement of medication adherence.
- Representing a wide variety of stakeholders covering industry, healthcare professionals, academics, patient groups, the consortium has reached a number of consensus positions. One of these is that while there have been many successful adherence initiatives, too often these fail to scale. One of the reasons for this is because they are not economically sustainable within the current ecosystem.
- The purpose of this paper is to state the consortium's understanding of the nature of the economic challenges surrounding adherence projects and suggests some possible routes forward.
- The views represented in the paper are the consensus view of the group, but cannot be taken as the position of any one organisation or individual.

Purpose of the paper

- This paper reflects a consensus view of the CfBI Medical Adherence consortium regarding the improvement of medication adherence, outlining the situation as the group sees it and suggesting next steps.

1 Centre for Business Innovation – see https://www.cfbi.co.uk/ for more details.

- The paper is envisaged as a record of the thinking of the consortium and to be used as a tool to aid to discussion between consortium members and other interested parties.

Audience of the paper

- Policy makers, regulators, health technology assessment bodies, HCPs, commissioners, professional bodies and their representatives, representatives of the healthcare industry, other adherence opinion leaders, , other key stakeholders, patients, and other interested parties.

An international perspective

- Poor medicine adherence is an international concern.
- The primary focus of this paper relates to the European perspective.

What do we mean by medication adherence

A definition

- There are many definitions of medication adherence. The consortium recognises the seminal nature of the 2003 WHO report "adherence to long term therapies: evidence for action" [2]. This uses the following definition of adherence to (long term) therapy:

  the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider

- Note that there are many definitions of adherence, each taking a slightly different perspective on the subject.
- We are specifically interested in adherence to medication. By medication we mean a therapeutic component that has been manufactured in some way. Thus medicines, medical devices and even some medical software would be forms of medication.
- While our focus is specifically on adherence to medication we recognise that adherence to all forms of therapy is important (but not the focus of this paper).

The elements of adherence

- Adherence itself is a very broad concept. When talking about adherence we should be clear what aspects of it we are concerned about. To help in this discussion we need further definitions of different components of medication adherence. The consortium uses those developed as part of the European ABC project (Ascertaining Barriers to Compliance) where adherence is broken into three components: initiation, implementation and persistence.
- These components are defined as follows (although note that this itself is a simplification): **Adherence** is the process by which patients take their medications as prescribed, composed of **initiation**, **implementation** and **discontinuation**. **Initiation** occurs when the patient takes the first dose of a prescribed medication. **Discontinuation** occurs when the patient stops taking the prescribed medication, for whatever reason(s). **Implementation** is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. **Persistence** is the length of time between initiation and the last dose, which immediately precedes discontinuation.[3]

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2 Sabaté, Eduardo. *Adherence to long-term therapies: evidence for action*. World Health Organization, 2003.

3 Vrijens et al., Br J Clin Pharmacol 2012; 73: 691-705 Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., ... & Matyjaszczyk, M. (2012). A new taxonomy for describing and defining adherence to medications. *British journal of clinical pharmacology*, *73*(5), 691-705.

Adherence is important and can be improved

"A worldwide problem of striking magnitude" [4]

- The WHO report quoted earlier states that poor adherence is "a worldwide problem of striking magnitude". This report refers to treatment for long term conditions, but the issue of poor adherence is encountered in many other parts of medication care.
- The consortium accepts that poor adherence is widespread, that it can lead to unnecessary expense to healthcare systems in their widest sense, that improving adherence will generally lead to improved health outcomes, and that it is possible to improve adherence.
- Indeed it can be argued that over the long term in some conditions non adherence becomes the 'standard' situation with patients who continue to reliably adhere to their therapy as being the outliers not the norm.
- This belief is backed up with an evidence base that the consortium has assembled.

Poor adherence has many causes

- The COM-B framework posits that an individual's Capability, Opportunity and Motivation influence their behaviour [5]. A review of quantitative [6] and qualitative [7, 8] reviews showed that COM-B is a useful way to group determinants of non-adherence [9]. Table 1 shows factors identified in reviews that are frequently associated with non-adherence across multiple long term conditions (reproduced from [9]).

4 Sabaté, Eduardo. *Op. Cit.*

5 Michie, Susan, Maartje M. Van Stralen, and Robert West. "The behaviour change wheel: a new method for characterising and designing behaviour change interventions." *Implementation science* 6.1 (2011): 42..

6 Kardas, P., Lewek, P., & Matyjaszczyk, M. (2013). Determinants of patient adherence: a review of systematic reviews. *Frontiers in pharmacology*, *4*, 91.

7 Nunes, V., Neilson, J., O'flynn, N., Calvert, N., Kuntze, S., Smithson, H., ... & Crome, P. (2009). Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence.

8 Pound, P., Britten, N., Morgan, M., Yardley, L., Pope, C., Daker-White, G., & Campbell, R. (2005). Resisting medicines: a synthesis of qualitative studies of medicine taking. *Social science & medicine*, *61*(1), 133-155.

9 Jackson, C., Eliasson, L., Barber, N., & Weinman, J. (2014). Applying COM-B to medication adherence: a suggested framework for research and interventions. *European Health Psychologist*, *16*(1), 7-17.

Table 1. *Applying COM-B to factors associated with adherence*

CAPABILITY	MOTIVATION	OPPORTUNITY
The individual's physical and psychological capacity to engage in the behaviour*	***All brain processes that energise and direct behaviour***	***All factors lying outside the individual that make performance of the behaviour possible or prompt it***
Psychological *Capacity to engage in necessary thought processes*	**Reflective** *Evaluations and plans*	**Physical** *Physical opportunity provided by the environment*
•Comprehension of disease and treatment •Cognitive functioning (e.g. memory, capacity for judgement, thinking) •Executive function (e.g. capacity to plan)	•Perception of illness (e.g. cause, chronic vs. acute etc.) •Beliefs about treatment (e.g. necessity, efficacy, concerns about current or future adverse events, general aversion to taking medicines) •Outcome expectancies •Self-efficacy	•Cost •Access (e.g. availability of medication) •Packaging •Physical characteristics of medicine (e.g. taste, smell, size, shape, route of administration) •Regimen complexity •Social support •HCP-patient relationship / communication
Physical *Capacity to engage in necessary physical processes*	**Automatic** *Emotions and impulses arising from associative learning and/or innate dispositions*	**Social** *Cultural milieu that dictates the way we think about things*
•Physical capability to adapt to lifestyle changes (e.g. diet or social behaviours) •Dexterity	•Stimuli or cues for action •Mood state/disorder (e.g. depression and anxiety)	•Stigma of disease, fear of disclosure •Religious/cultural beliefs

*statements in italics represent definitions given by Michie et al. (2011)

Poor adherence is widespread and expensive

- 50% of medications for chronic disease are not taken as prescribed [10].
- This costs the US healthcare system $ 100 billion to 290 billion annually [11]
- In addition, a $474 -650 billion USD avoidable cost opportunity, or 8-10% of the world's health expenditure, exists in these areas" [12].
- It is estimated that 125,000 deaths in the US and 200,000 deaths in Europe annually are due to nonadherence [13].

10 Sabaté, Eduardo. *Op. Cit.*

11 Rosenbaum, Lisa, and William H. Shrank. "Taking our medicine—improving adherence in the accountability era." *New England Journal of Medicine* 369.8 (2013): 694-695.

12 Moore, T., Chawla, S., and Firlik, K. "Estimated annual pharmaceutical revenue loss due to medication non-adherence." *Capgemini Consulting & HealthPrize Technologies. Available in http://www. adherence564. com/, accessed February*: 2017.

13Pharmaceutical Group of the European Union "Targeting Adherence - Improving Patient Outcomes in Europe through Community Pharmacists' Intervention" *PGEU policy statement on adherence to medicines* 2008.

- 10% of hospitalizations are due to incorrect use of medications

Numbers are often top down estimates but those figures make medication adherence a top priority for healthcare budgets across the world.

Improved adherence is possible and improves health outcomes

- There are many reasons why patients are non adherent (some papers identify 700 [14]). There is thus no one solution fits all approach and there is a need to understand and quantify the problem in each individual patient. To this end, the following approach is best suited:
    - Use the ABC taxonomy to define which element(s) of medication adherence you are interested to tackle.
    - Use reliable and precise measure of adherence to address the elements of medication adherence you are considering.
    - Perform sound investigations/analysis to quantify the problem, identify the cause(s) and consequence(s)
- Feeding back this information to the patient has proven to be the most effective approach to remove the root cause and maintain the gain over long period of time [15]. Every meaningful initiative to manage medication adherence should work if it is applied to the right person, for the right problem, at the right time.
- The WHO stated that any intervention to improve medication adherence to existing treatments would have a greater benefit than the development of new drugs for most medical conditions [16].

Measurements and Interventions

Measurement

- In order to demonstrably improve adherence we need to be able to measure it. There are many different measurement techniques each with their own advantages and disadvantages, and each appropriate to different types of usage. Examples of adherence measurement techniques include: patient reported including validated questionnaires, directly observed (by a healthcare professional), prescription monitoring (by comparing prescriptions made with prescriptions collected), and a variety of technological measurements such as 'Medication Event Monitoring Systems (MEMS – including intelligent pill packets, inhalers, sharps bins and other devices), wearables and ingestible devices.
- In monitoring adherence, it should also be recognised that accurate assessments of "control groups" are difficult, because in many cases the act of monitoring itself impacts on the patients underlying medication taking behaviour – thus over-estimating adherence in control groups

14 Kardas, Przemyslaw, Pawel Lewek, and Michal Matyjaszczyk. "Determinants of patient adherence: a review of systematic reviews." *Frontiers in pharmacology* 4 (2013).

15 Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., ... & Matyjaszczyk, M. (2012). A new taxonomy for describing and defining adherence to medications. *British journal of clinical pharmacology*, *73*(5), 691-705.

16 Sabaté, Eduardo. *Op. Cit.*

- It is not the purpose of this paper to discuss these in detail but other than to observe that measurement techniques vary from simple to complex – with the corresponding impact on the
- cost of such measurement. It is not the case that more complex is necessarily better however, and the appropriate measurement technique needs to be chosen so that it is appropriate to the situation.

Intervention

- In order to improve adherence there must be an intervention to effect a change. Again, there are many intervention techniques. Examples include simple reminders (by text, phone or app notification), increased patient 'activation' and 'engagement' through improved self monitoring of condition and therapy, automated dispensers, enabling the patient's healthcare professional to better understand the level of adherence leading to a shared approach with the patient (sometimes called concordance), and other still richer approaches to affecting behavioural change.
- It is not the purpose of this paper to discuss these in detail but as with the approach to measurement, typically the more successful intervention techniques are also the more complex and costly. For a comprehensive review of the efficacy of adherence interventions the reader is referred to the Cochrane review on the subject [17].

Adherence Initiatives

- There is no single or even dominant approach to measuring and improving adherence. Efforts have been fragmented to date and tend to be project based – often wrapped up in larger programmes looking at improving patient support, or patient engagement, in a more general sense (through the use of Patient Support Programmes – PSPs).
- This paper refers to any activity that aims to improve adherence directly or as part of a larger activity as an **adherence initiative**. This may be discrete projects or more open ended long term services. The focus of the paper is on the commercial sustainability of adherence initiatives, whatever their form.
- Adherence initiatives are delivered by a variety of organisations including health care bodies, patient support consultancies, pharmaceutical companies, pharmacies, healthcare charities, technology providers and many others. Adherence initiatives are sponsored by a variety of organisations including the above but adding additional stakeholders such as carers, patients themselves, insurance companies, the healthcare system.
- While there are many potential sponsors and contributors to adherence initiatives, the most common major sponsors currently are pharmaceutical companies and some health systems via the funding of pharmacist-led interviews. We argue that in some important examples of adherence improvements it is not reasonable to expect industry to provide the funding. This can lead to potentially beneficial activities (from a patient / carer and public health perspective) being overlooked.
- It should be stated that effective adherence activities need to operate in a very complex and heavily regulated environment and as such are often complex, constrained, and expensive to run.

17 Haynes, R. Brian, et al. "Interventions for enhancing medication adherence." *Cochrane database syst Rev* 2.2 (2008).

Benefits of Adherence

- There are many stakeholders in the healthcare system – a number are listed below. We believe that each type of stakeholder benefits in different ways from increased adherence. Some of the benefits as we see them are listed below.
- Patients and carers
    - Improved health outcomes, better understanding of and engagement with own healthcare, reduced side effects (though the selection of agreed and appropriate therapies), reduced anxiety for carers.
- Employers
    - Healthier more capable workforce, reduced sick leave (and expenses / productivity penalties associated with this)
- Pharmacy
    - Increased loyalty and interaction with patients, increased social value of community pharmacy, opportunity to increase level of service by pharmacist
    - business from and interaction with patients, opportunity to increase level of service provided by pharmacist
- Health Care Professionals
    - Improved health outcomes for patients, reduced cost of healthcare provision (though better management of conditions), increased quality of care, improved engagement with patients
- Pharmaceutical companies
    - Improved health outcomes, enhanced brand, alignment with move towards value based pricing and post marketing surveillance to support claims and ensure patient safety to approved regimes.
- Tech / Device / Service providers
    - Increased innovation, measurement of adherence leading to more sophisticated products, increased adoption of products
- Medical Research
    - Improved clinical trials, reduced cost (through the need for fewer trial participant's), reduced risk of trial failure (see for example [18] or [19] or [20])
- Regulators / Industry standards bodies
    - Improved health outcomes, increased quality of care.
- Governments
    - Reduced cost of healthcare provision, reduced sick leave with resultant benefits for economy

18 Breckenridge, Alasdair, et al. "Poor medication adherence in clinical trials: consequences and solutions." *Nature Reviews Drug Discovery* 16.3 (2017): 149-150.

19 Marrazzo, Jeanne M., et al. "Tenofovir-based preexposure prophylaxis for HIV infection among African women." *New England Journal of Medicine* 372.6 (2015): 509-518.

20 Breckenridge, Alasdair, et al. "Poor medication adherence in clinical trials: consequences and solutions." *Nature Reviews Drug Discovery* 16.3 (2017): 149-150.

- Patient advocate groups
    - Improved health outcomes for members
- Insurance companies
    - Reduced cost of insurance provision related to sickness cover – resulting in lower premiums
- Government / the taxpayer
    - Healthier workforce leading to reduced unemployment, reduced social security payments, and greater economic activity.

Why is improving adherence difficult

Very complex – many impediments to improvement

- If it is accepted that poor adherence is widespread and expensive, that improving adherence is possible and that in many cases this leads to improved health outcomes, then why does poor adherence remain so common? The consortium believes this is because the causes of poor adherence are complex and varied, and that this complexity precludes simple solutions.
- The complexity – and the difficulty associated with finding sustainable 'solutions' can be split into the 'essential' and the 'structural'.
- poor medication adherence is inherent in the nature of patient's relationship with their medicine
- The **structural** complexity of poor medication adherence is related to the way that the healthcare environment is currently structured
- The consortium feels that the complexity ecosystem needs to be characterised if any progress is to be made in the reduction of poor adherence, but that some of the structural complexities need to be addressed before any large scale changes in adherence will be possible.
- Some of the key essential and structural complexities are laid out here.

Essential complexities and impediments

- Listed below are some of the aspects of the essential complexity of poor adherence as understood by the consortium. It should be emphasised that all the areas listed below – and many more – are the subject of much analysis and debate and progress. However, the essential complexity of the adherence environment is one of the causes of slow progress in the field.

Intentional vs non intentional

- Although a simplification of a complex situation it is sometimes useful to consider whether poor adherence is unintentional or intentional. Unintentional non-adherence means that a patient has not adhered to their therapy, but they want to - intentional non-adherence means that a patient has not adhered to their therapy because they do not want to.
- A significant amount of poor adherence can be considered to be intentional. Interventions which address intentional non adherence are often more complex than those that address unintentional non adherence.
- It should be noted that in reality the situation is much more complex with significant overlap between intentional and unintentional adherence.
- People change over time – need to almost certainly address both factors to be successful

Behavioural / belief influences

- Much of the intentional non adherence is linked to the patient's beliefs in the necessity / urgency (or lack thereof) of the requirement for the therapy in question. Belief-based intentional non-adherence is itself very varied, reflecting the many belief systems that people have, as well as reflecting differences associated with different conditions, different therapy types, and even different regional norms and customs. Need to include concerns in here too

Difficulty of measurement

- Measuring the improvement in medication adherence for a particular intervention can be difficult. There seems to be no 'Gold standard' approach to measurement although some approaches are more robust than others. It is reasonable to assert that in general the more robust methods can be very expensive, while more cost-effective measurement techniques can be less reliable (although there is an argument that 'good enough' is better than nothing which is too often the alternative). It should be noted that it is difficult to have an effective control group for adherence studies with a considerable placebo effect adding further complications to study design.

Importance of therapy 'feedback'

- It is considered that population adherence rates are impacted when there is some visibility of treatment effect (both positive visibility as in the experienced lessening of symptoms and negative visibility as in the experiencing of negative side effects). Medications that have no immediately observed benefits (such as statins) often have worse adherence.. However, it is typically observed that adherence trends are similar with adherence dropping off at a comparable rate over time albeit from a higher base where there is some feedback.

Structural complexities and impediments

Economic complexities

- The consortium believes that the most fundamental structural impediment is that there is a mismatch between individual, commercial, and social value of adherence activities. The market does not function smoothly, due to the commercial reward for improving adherence not being aligned to social value or (perceived) personal value that improved adherence will generate. It should be said that the mismatch can work both ways – something that we will investigate in this paper.

Regulatory impediments

- Medication adherence activities operate in a highly regulated environment. While vital to the safe delivery of what is a complex medical intervention we argue that there is space to streamline these so as to reduce the cost and complexity of creating adherence solutions while maintaining the required level of patient safety.

An adherence 'market'

A large problem

- We have seen above that the WHO describes the poor adherence as being "A worldwide problem of striking magnitude". Not only is poor adherence to long term medications common, it is also expensive. We need to look at who bears the expense.
- There are many stakeholders in the healthcare system. The group has considered organisations from sectors represented in the following diagram:

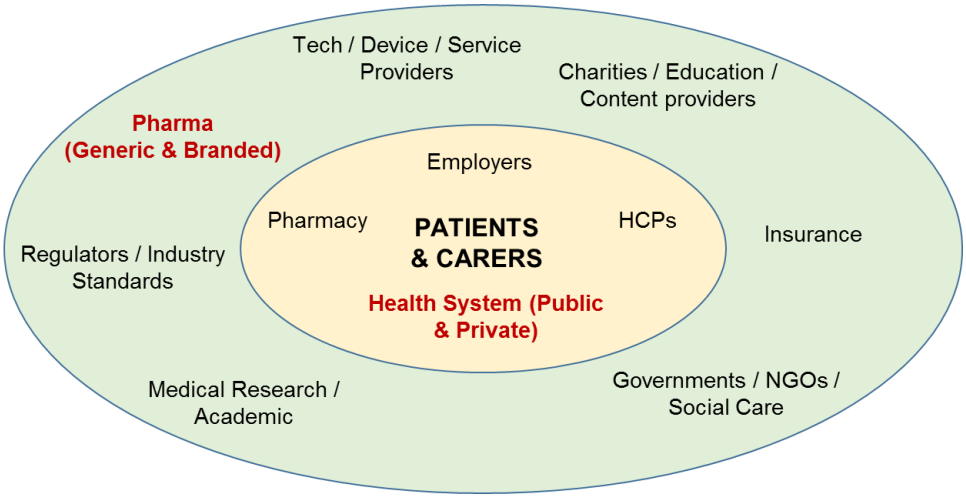

Figure 1: Stakeholders with an interest in adherence, representing individual, commercial, and social beneficiaries of improved adherence.

- Each of these players has a role to play in improving adherence, each gaining differing (financial and other) benefits.
- The cost of poor adherence – and the potential benefit associated with its improvement – is difficult to state with confidence and there is little literature relating to this. Some efforts have been made to estimate the cost to two of the stakeholders indicated above. These are (highlighted in orange above) pharmaceutical companies and the (public or private) health system.
- In 2004 Di Matteo [21] estimated the annual cost of poor adherence to the US health care system (through readmissions and other complications arising from poor therapy adherence as well as the cost of wasted health care professional time) as being $300 bn (this translates to around $900 bn globally – the US accounting to around a third of global healthcare expenditure). Other more in depth studies suggest lower but still significant numbers with Trueman suggesting annual costs in the UK as being many hundreds of millions of GBP [22]
- More recently, a report written by Cap Gemini and Health Prize [23] estimates the cost to the pharmaceutical industry (primarily through lost revenue associated with non provision of drugs) as being as high as $637 bn per year globally.
- The cost of poor adherence is very difficult to identify with absolute precision but it is clear that it is high for health care systems and pharmaceutical companies.
- Note that the costs of poor adherence go beyond these simple measures for all stakeholders and cover more difficult to measure quantities such as reputational damage and frustration of the drug and therapy discovery process.

21 DiMatteo, M. Robin. "Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research." *Medical care* 42.3 (2004): 200-209.

22 Trueman, Paul, et al. "Evaluation of the scale, causes and costs of waste medicines. Report of DH funded national project." (2010).

23 Moore, T., Chawla, S., and Firlik, K. "Estimated annual pharmaceutical revenue loss due to medication non-adherence." *Capgemini Consulting & HealthPrize Technologies. Available in http://www. adherence564. com/, accessed February*: 2017.

Industrial companies as drivers (and sponsors)

- The studies demonstrate that there are instances where there is a clear incentive for industry (particularly pharmaceutical companies) to implement initiatives designed to improve adherence, though the comparative lack of Pharma generated peer reviewed reports into the impact of non-adherence may indicate that the revenue lost to non-adherence is over-estimated by consultancy generated reports. Adherence initiatives and patient support programmes are indeed often funded by pharmaceutical companies acting to support individual products (around the pill) or therapies (beyond the pill) services.
- Even though regulations often restrict their engagement with patients, other key stakeholders can have greater influence over patients in their treatment journey.
- Despite this, in discussions it seems that there is often an expectation from payers and providers that it should be pharmaceutical companies who fund the majority of adherence initiatives.

Pharmacy as a potential big player.

- Most patients and their carers interact frequently with pharmacies to have their drugs dispensed and pharmacists are seen as healthcare professionals who are 'therapy experts' by the general public. The consortium believes that pharmacies should take a larger role in adherence management via multichannel interventions. The intensity of the intervention will vary with the strategy adopted within a given pathway.
- Pharmacists interact in a multi-channel way (face to face or digitally) and are in a position to provide accurate advice to patients. Experience from across Europe shows that pharmacists have been incentivised to take a more active role in the medication management of their patient population (eg Medicines Use Review in the UK and the anticoagulant interview in France).

Value Misalignment

- It is clear that the costs of poor adherence are significant (to all stakeholders). However, the commercial activity addressing this market is comparatively small. This is a sign of economic value misalignment – where supply is not meeting demand (sometimes called 'market failure')..
- There are many causes for this misalignment of economic value. Some relate to the essential complexity of the causes of poor adherence (as touched earlier in the paper). The consortium does not feel qualified to pass judgement or make any observations here. There are also causes related to the structural complexity. In particular the consortium argues that there is a significant and vital set of adherence activities that cannot be undertaken, driven, or funded by pharmaceutical companies alone, but should be delivered from within the healthcare eco-system with all parties around the patient playing a part.

The adherence landscape and value misalignment

- The economic aspects of adherence initiatives vary greatly, depending on the nature of the condition, the therapy, and other characteristics of the patient and healthcare environment. The economics surrounding the improvement of adherence a high cost new specialist therapy is likely to be very different to that relating to a low cost therapy for a long term condition.
- To better understand the different economic adherence 'scenarios' the consortium suggests placing them on a 'landscape' created by considering dimensions pertinent to adherence initiatives.
- The CfBI Medical Adherence consortium has considered many approaches to understanding and describing the adherence 'market'. The one gaining most widespread consensus is also the simplest considered.

- It is hopefully clear that the group recognises the great complexity and diversity of opinion surrounding the subject of adherence. In order to make the argument presented in this paper many simplifications have been made. The consortium believes that these simplifications are necessary to lend clarity to the argument and that they do not invalidate it.

Condition / medication pairs

- The success and commercial viability of adherence activities can be best understood by considering condition / medication pairs.
- Adherence initiatives typically focus on condition and medication pairs (one or several).
- Adherence profiles in a population to a given treatment are likely to vary according to the condition for which it is prescribed. Equally different medications – with their own side effects – will have differing adherence 'profiles'. Clearly this step, while useful, is a simplification and within a single condition and therapy we will see a wide variation of adherence characteristics.
- Examples of condition medication pairs might be Type II diabetes and Metformin, or Paroxetine for depression.
- We can place condition medication pairs on a quadrant that the consortium believes characterises the market sustainability of a particular adherence activity.
- There are two key dimensions that describe (at a high level) the economic viability of adherence activities: the unit cost of the medication (high or low) and the total social impact of the condition. Total social impact refers to the impact to society as a whole of the condition. This means that rare conditions, while possibly devastating to the individuals suffering with them, are unlikely to have as big a social impact to society as a whole as common conditions.

Unit cost of medication > Total social impact (of condition) V	High	Low
High		
Low		

- Where the unit cost of the medication is high there is a commercial justification for manufacturers to invest (directly or via third parties) in adherence initiatives as these will the commercial benefit from increased sales will be sufficient to fund the initiative. This is the green column. Where the unit cost of the medication is low there is less commercial justification to bear the cost and risk of adherence activities (which as we have seen above can be significant) – the financial benefit in terms of increased sales will not justify the cost of the adherence intervention. This is the red column.
- It should be pointed out that although true in the round, this argument is a simplification and there may be other indirect benefits for industrial companies of increasing adherence such as brand enhancement. This might have the effect of increasing the benefit – and thus commercial return – of some adherence activities that might otherwise have been deemed uncommercial.

This effect, while real, is marginal when compared to the large costs and benefits outlined above.

- The top and bottom rows refer to the total social impact of the condition. When a condition is serious and widespread we can say that it has a large total social impact. When the condition is widespread but less serious (such as a common cold) or is serious but not widespread, then the total social impact of the condition is (comparatively) low. Improving adherence to medications for conditions where the social impact is high has the potential to be of great benefit to society. The top row represents conditions with high total social impact – this is indicated with cross hatched shading in the diagram above.
- Measuring the social impact of a condition – or more specifically the social impact of increasing adherence to medication being prescribed for a condition – will be difficult to establish with any precision. Indeed, the social impact goes beyond the cost to the payer in the healthcare system but will expand to a wider view of society and take into account increased social security payments associated with poor health and other externalities.
- The red shaded quadrant of the grid (the quadrant with a think blue border) is where there is a great public health benefit in increasing adherence, but little incentive for the manufacturers – or other commercial members of the therapy delivery chain – to fund interventions that improve adherence. This quadrant is where there is the greatest misalignment of value in the delivery of improved adherence.
- A number of condition / therapy pairs are added to the grid below – those in the quadrant outlined in blue are those where we see the greatest misalignment of value.

Unit cost of medication > Total social impact (of condition) V	High	Low
High	Anti TNF medications for arthritis	Anti-depressants targeting mental health conditions Metformin for diabetes Common medications targeting breast cancer
Low	New medications targeting hepatitis C New medications targeting cystic fibrosis	

- The blue quadrant lists exemplar conditions and medications where the public health benefits from increased adherence are great, but there is little justification currently for commercial organisations to implement the necessary projects that would help achieve this.
- One further point that can be made is that failure to adhere to medications often leads to a condition deteriorating. Treating advanced unmanaged conditions tends to require more sophisticated treatment regimes (and more costly medications) than un advanced well managed conditions. Looking at the adherence 'landscape' we would see a patient move from the top right to top left quadrant with medications – and thus cost of treatment – becoming more expensive. This can be viewed as an economic disadvantage to pharma companies for encouraging adherence further reducing the commercial reward for improving adherence in this quadrant.

Summary

- The consortium feels that there is often a mismatch between individual, commercial, and social value of improving adherence. This is reflected as an economic value misalignment where a demand is not met by supply.
- The consortium feels that the greatest economic value misalignment is observed where
    - The social impact of the condition is HIGH, and
    - The unit cost of the medication is LOW.
- The consortium believes that improving adherence in condition / medication pairs that satisfy this description can result in significant improvements in health outcomes for the patient population but that there are insufficient commercial drivers for industrially driven adherence activities.
- For medications and conditions that satisfy these criteria the current market (where industrial companies are expected to 'drive' adherence improvements) is not providing and will not provide a sustainable improvement in adherence.
- In addition to addressing the economic value misalignment outlined above, steps should be taken to reduce the cost of adherence initiatives. One way of doing this is to tailor regulation so as to better support activities to improve adherence. This is discussed later on in this paper in the section titled "Reduction of cost – the role of regulation".

Recommendation

- The consortium observes that there is often a mismatch between individual, commercial, and social value of improving adherence.
- The consortium recommends that policymakers and influencers concentrate on addressing the area of greatest economic value misalignment for adherence initiatives – namely where the volume of prescriptions is high, and cost of drug is low – and focusing on those medications and conditions where non adherence is considered a significant problem.
- Only once this economic value misalignment is addressed will innovative solutions emerge and flourish leading to improved adherence.

Approaches to economic sustainability

Requirement for funding

- The consortium feels that there is often a mismatch between individual, commercial, and social value of improving adherence. Specifically, where the condition and medication is such that the social impact of the condition is high, and the unit cost of the medication is low then the market as it currently is will not lead to successful adherence initiatives and yet the benefit to public and individual health can be very high.
- The consortium believes that in these situations, payment for adherence improvement initiatives and activities cannot come from pharmaceutical companies alone, but must come from the whole ecosystem including other major beneficiaries of improved adherence. This may include – but is not limited to – the public health system.
- Funding should be sought from the individual, commercial, and social stakeholders as referenced in figure 1.

Business model innovation

- We have argued that there are some combinations of condition and therapy where it should not be expected that industry fund adherence initiatives. Equally it seems unlikely that public health payers will significantly increase the level of funding for these initiatives. Making successful adherence activities truly economically sustainable will require the development of new business models. Indeed, creative business model innovation is needed to make the adherence related solution innovation sustainable.
- The consortium has discussed the GAVI vaccine alliance and recent work on antimicrobial resistance as areas where there has been funding innovation.
- Funding vaccines – the GAVI approach
    - GAVI, the Vaccine Alliance, is a public private partnership dedicated to increasing the access to vaccines in the developing world. It supports the development and distribution of affordable vaccines to poor countries through a number of mechanisms including
    - Matched funding – contributions to the vaccine fund are matched by a fund contributed by developed country governments and charitable bodies (predominantly the Bill and Melinda Gates Foundation). This has raised hundreds of millions of dollars of contributions.
    - Vaccine bonds (International Finance Facility for Immunisation) –long- term donor pledges (a mix of developed and developing country governments) are used to issue vaccine bonds on the capital markets. This has raised several billion dollars, helped develop new vaccine markets, and is estimated to have saved over 2 million lives to date
    - Advanced market access – donors (governments and large charities) guarantee a price for vaccines ensuring there is a known market to develop for.
- New business models helping the fight against antimicrobial resistance
    - As part of the 'The review of antimicrobial resistance' commissioned by the previous UK prime minister a recent paper 'Rapid diagnostics: stopping unnecessary use of antibiotics' [24] it is observed that there is a 'Mismatch between individual, commercial, and social value of using diagnostics' (a similar situation that we maintain applies to the area of medication adherence we are concerned with).
    - The review argues for the use of 'Market Stimulus' pots. These funds are to be set up by central (generally state) bodies and would act to provide additional revenue to ensure that the stimulated activities are commercially attractive. In the words of the review "[Market Stimulus Pots] would not pre-judge which [solutions] are best, rather they would follow the success of actual products bought by healthcare providers, by topping up the payments to developers to make sure the commercial benefits and the needs of society are better aligned". The 'Market Stimulus' pots would thus act to create a subsidised (and commercially viable) market.
    - It is possible that a similar approach might work in the case of adherence initiatives. The source (s) of funding for these 'Market Stimulus' pots has not been identified by the consortium. Specifically, it should not be assumed that funding should come from central government: as has been explained there are many beneficiaries from improved adherence.

24 O'Neill, J., 2015. Rapid diagnostics: stopping unnecessary use of antibiotics. *Review on Antimicrobial Resistance*

- While some or all of these mechanisms may be inappropriate to the development of a sustainable market for adherence initiatives they illustrate some innovative approaches to increasing economic sustainability in other health markets.
- The way in which the economic value misalignment (for improving adherence where volume of prescriptions is high, and the cost of the therapy is low) needs further consideration and discussion with a wide set of stakeholders.
- The consortium believes that whatever approach is adopted, it should be accessible to a broad set of suitable providers of solutions who are active in the eco-system which could lead to increased innovation in addressing poor adherence from new participants in the market.
- The consortium further believes that funding models should avoid limiting funding by criterion so that only a small number of projects and initiatives are considered for funding. This 'silo solution' approach can act to prevent the emergence of truly inter-disciplinary and innovative approaches.

Measurement of Benefit

- However funded, the payment – and commercial return – for a successful adherence initiative is likely to be aligned to service sector margins rather than innovative pharmaceutical margins.. As such the approach for gaugingefficacy and effectiveness based on the improvement in health outcome is not applicable to adherence interventions in the same way it is to drug interventions.
- The consortium argues that it is important that any adherence intervention can be shown to improve health outcome. However the lower level of risk associated with adherence interventions for medications that have already been proven through the clinical trial process (as opposed to the risk associated with the medications themselves) means that the burden of proof for improved outcomes can be lower than it is for the underlying medication. The usage of a representative sub-population should become the reference as the measurement of the adherence level of an entire population can also be costly.
- The consortium acknowledges that the precise value that can be ascribed to improved adherence is difficult to derive and will vary according to measurement techniques and availability of relevant clinical evidence. There is clearly still much work to do to understand the health outcomes linked to improved adherence and the approach to measuring this.

Recommendations

- The consortium recommends that stakeholders identify appropriate and innovative funding mechanisms and take steps to implement these. This will increase the economic sustainability of adherence activities where the social impact of the condition is high and the unit cost of the medication is low.
- The consortium recommends that it is recognised that there should be a reduced burden of proof for improved impact for adherence activities compared to that for the underlying medication.
- The consortium also recommends that any new route for accessing funding to support adherence initiatives be made clear by bodies responsible for setting compensation rules. By making the pathway for accessing funds clear it will be easier for new organisations to start offering services in this area.

Reduction of cost – the role of regulation

Regulatory burden and costs

- In the previous section we argue that for certain types of adherence initiative, the existing market structure will not provide a solution and central public health funding is required. However, to increase economic sustainability it is equally important to look at reducing the costs of adherence activities.
- There are many aspects of cost associated with adherence initiatives. Those that the consortium is particularly focussed on as a group are those flowing from regulatory compliance.
- Aspects of regulation related costs include
    - **Regulatory complexity** – regulations of adherence activities vary greatly between regions, the nature of the intervention, and by who is funding the activity.
    - **Regulatory burden** – it is felt that it is time consuming and costly to implement an adherence programme (often as part of a larger patient support programme) because of the regulatory and compliance requirements that need to be satisfied, and that if this burden can be reduced safely the number of viable adherence interventions will increase.
    - **Regulatory obstruction** – it is felt that some regulations do not just make adherence initiatives difficult but actively prevent them from working effectively (these regulations are typically related to a control on patient communication – to both the individual and the population at large).
- It must be reiterated that the consortium feels that it is vital that patient safety be maintained through effective regulation. However the consortium believes that some of the costs described above are accidental and have come about because regulators have historically not considered increasing adherence to be a priority.
- The consortium believes that regulators should now start thinking explicitly about issues relating to adherence.
- The consortium has an activity aimed at introducing (measurement and reporting of) adherence into the formal and informal regulations relating to the running of clinical trials. A working group is focussed on this aspect of adherence and has led to the writing of a published paper on the subject [25].
- The consortium thinks that regulators should work in partnership with stakeholders representing patients and carers, providers and industry to focus regulation so that it enables more initiatives, whilst still ensuring a level of quality in maintained.
- The consortium thinks that other stakeholders should be more proactive in engaging with the regulators at earlier stages as advance knowledge will help the regulators adapt more quickly and increase the likelihood of useable standards that encourage success for all.

25 Breckenridge, Alasdair, et al. "Poor medication adherence in clinical trials: consequences and solutions." *Nature Reviews Drug Discovery* 16.3 (2017): 149-150.

Recommendation

- The consortium recommends that regulators, industry, payers, health service providers, patient and carer representatives and other stakeholders work together to
    - recognise the importance of increasing adherence, and take this into account when drafting regulations.
    - clearly identify ‘best practice’ as well as ‘minimum requirements’ to guide existing and new organisations operating in this market.
    - Encourage more engagement between the stakeholders in the value chain to work together on standards that meet the regulatory requirements, are usable in practice and reduce the barriers to encourage innovative approaches to be tested and validated.

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