SCIENTIFIC AND ETHICAL CHALLENGES TO DEFINING WHAT CONSTITUTES 'PROPORTIONATE EVIDENCE' FOR THE REGULATION AND ACCREDITATION OF APPLICATIONS TO TREAT ADDICTION

There are important scientific and ethical challenges to defining what constitutes 'proportionate evidence' for the accreditation and prescription of apps to treat addiction. Potential unintended consequences include issues of opportunity costs, whereby the use of low-quality apps may delay the use of effective support. Conversely, heavy-handed regulation could stifle innovation if it deters developers from adding new components if each change required another expensive and time-consuming trial.

'Economists and doctors talk about "opportunity costs", the things you could have done, but didn't, because you were distracted by doing something less useful' [1].

In their *Addiction* Opinion and Debate article, Khadjesari *et al.* [2] draw on examples from the United Kingdom, Australia, the United States, Canada and Germany to discuss the benefits and potential pitfalls of two emerging approaches to the regulation of applications (apps) to treat addiction—the classification of apps as medical devices (which may lay the foundation for a prescription model) and the accreditation of apps by trusted public health organisations. These much-needed reflections raise challenging scientific and ethical questions as to what constitutes 'proportionate evidence' for these apps to be listed on curated portals endorsed by public health bodies or prescribed by healthcare professionals.

It is clear from the helpful description of a range of regulatory frameworks by Khadjesari *et al.* [2] that stakeholders appear to—at least for now—have converged on the view that evidence from a randomised controlled trial (RCT) is not necessary for the accreditation or prescription of low-intensity apps (e.g. those that solely incorporate strategies such as goal setting or self-monitoring) [3,4]. Regarding diagnostic apps, multi-component preventive behaviour change apps or those targeting vulnerable populations, 'best practice' requires RCT evidence [3] but is not required for accreditation or prescription [3,4]. Instead, a range of study designs (with different strengths and weaknesses) are considered acceptable as long as there is an appropriate comparator. Such a 'proportionate evidence' approach may have initial face validity: most apps are unlikely to cause serious harm and given that an app's effectiveness depends largely upon the context in which it is implemented (e.g. how it is introduced to users and in what setting); this may limit the generalisability of traditional RCTs [5]. However, it is important not to discount potential unintended consequences of such an approach, including issues of opportunity costs. The lack of success with a low-quality app may deter people from future use of behavioural support or delay the use of effective support at critical time-points, potentially making the condition more resistant to change or failing to prevent serious drug-related harm, such as neglect or suicide [1,6]. Those working in the service of public health (and whose practices are supported by taxpayers) have a duty to promote evidence-based support.

Considering the agile and rapidly evolving nature of apps to treat addiction, regulators also need to set clear criteria for determining when available evidence is outdated. Heavy-handed regulation could stifle innovation if it deters developers from updating software or adding new components if each change required another expensive and time-consuming trial. Although the German *Apps on Prescription* framework requires developers to declare 'significant changes' to apps listed in their directory, exactly what constitutes a significant change and what actions should be taken in order to maintain one's listing is determined on a case-by-case basis [4]. In addition, although still relatively rare, future iterations of apps to treat addiction are likely to be underpinned by unsupervised machine learning algorithms without human oversight [7]. It remains unclear what 'proportionate evidence' may look like for apps underpinned by adaptive algorithms which learn from previous users [3,4].

Mohr *et al.* [8] argue that clinical trials of health apps could have increased impact if focusing on the evaluation of 'intervention principles' (as opposed to a specific instantiation of an app), as this would allow for ongoing quality improvement without undermining prior evidence. In addition, innovative study designs linked to the multiphase optimisation strategy (MOST), including factorial screening experiments, sequential multiple assignment randomised trials (SMARTs) and micro-randomised trials (MRTs) [9,10] are particularly suited to supporting continuous optimisation and evidence-generation, important for the safe and meaningful accreditation and prescription of addictive behaviour apps.

The wider potential consequences of different regulatory approaches need to be continually monitored and reviewed. Although prescription models may increase access to evidence-based support, they may inadvertently lead some groups to having reduced treatment access due to a lack of health insurance, stigma of help-seeking in person or through perpetuating notions that addiction is a brain disease [11] which requires prescribed treatments.

In sum, concerted efforts from scientists, healthcare professionals, end-users and policymakers are needed to make progress on what 'proportionate evidence' should look like for the accreditation or prescription of different categories of apps to treat addiction, including what

constitutes a 'significant change' following initial evidence generation and how to manage apps with adaptive learning algorithms.

Declaration of interests

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