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COMMENTARY

Impact of a Global Pandemic on Health Technology Assessment

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1 Unprecedented Times

The COVID-19 pandemic will have unprecedented impacts on individuals, healthcare systems and economies worldwide. The exponential growth of infected individuals [1] will soon be matched by the growth rate of scientific literature [2] on: the disease mechanism [3], transmission dynamics [4], prevention strategies [5], treatment [6], consequences for other diseases and their management [7], other health and/or social impacts [8], public health impacts [9, 10] and the economic impacts [11].

As healthcare systems turn their entire attention to 'fighting this war' [12], it will not be without casualties in other parts of the system. This commentary offers some insights on what the COVID-19 pandemic specifically means for health technology assessment (HTA) given the extreme measures that governments have taken to 'flatten the curve' and treat the affected. COVID-19 will change life as we know it, but as we adapt so will our approach and it is likely that HTA will similarly adapt to this shock.

2 Health Systems: Crisis Precipitates Change

Caring for people with COVID-19 has overwhelmed hospitals and health centres: there are capacity constraints on the number of critical care beds, the number of ventilators, and the ability to test for active infection with the virus and evidence of antibodies reflecting previous infection. Worldwide healthcare systems have responded with an 'all hands on deck' approach. Clinicians, nurses, allied health and public health professionals, students, and retired staff are being retrained and deployed to join the frontline in the face of increased patient numbers and absences among healthcare workers. Routine non-urgent surgery and outpatient appointments have been postponed or cancelled [13, 14] and clinicians are using telemedicine to provide care remotely [15]. This is to minimise transmission in the public, to protect the healthcare workforce and to manage staff shortages.

3 Clinical Trials in Lockdown

A consequence of this is that most clinical trials and other research involving patients and healthcare professionals, not directly related to COVID-19 (e.g. RECOVERY [16]), have been suspended [17]. There is little if any enrolment into new studies, other than those directly related to COVID-19, and follow-up of patients on current trials will be curtailed or adapted. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued guidance on what study sponsors should do if protocol deviations are required to ensure patient safety while preserving study integrity and the quality of the data [18, 19]. Amendments to protocols may involve alternatives to in-person visits for patient evaluations including phone or virtual visits or locations other than hospitals or health centres.

Depending on the extent and the duration of the pandemic, clinical trials that are not specific to COVID-19 prevention, testing or treatment will face increasing difficulties. This will mean that any resulting evidence base will be uncertain, trials may not be powered appropriately if they did not recruit the required sample size, there will likely be more missing data than normal owing either to a loss of follow-up or for example patient notes being held in a locked down building, and clinical measures may be replaced with patient-reported outcome measures. The implications of this situation includes missing real treatment effects for underpowered studies, or erroneously declaring a treatment effective based on a surrogate endpoint.

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4 Research and Development in Hiatus

Different countries (including different states within countries) are taking different approaches to limiting the spread of the virus; at the time of writing, ~25% of the world's population is effectively in lockdown. For example, in the San Francisco Bay area, a 'shelter in place' order restricts individuals to their homes, but allows for people involved in 'health care operations', including the employees of biotech and pharmaceutical companies, to travel [20]. Government guidance aside, many companies acted early and self-imposed social distancing and remote working on their employees if their roles allowed it; for example, the only research that can take place on University College London campuses is that which is in the immediate national interest, i.e. research on COVID-19 [21]. Pharmaceutical and medical technology companies are also prioritising their research and development towards COVID-19, working on diagnostic tests, vaccines and/or therapies [22]. Given this and that most new technologies are developed onsite in laboratories, COVID-19 will likely impact the development of future technologies. Delays this year in discoveries and initial experiments may not be evident until a decade later given the length of time to get innovations to market.

A further impact of COVID-19 is that COVID-19 studies have inundated many research ethics committees, and these are taking priority over other research projects (personal communication). It is also likely that these committees may be under-resourced if clinically trained members have been redeployed.

5 Approval and Launch Delays

In the short to medium term, COVID-19 may delay both technology approvals and the launch of products. Just as many people have adjusted to working remotely, regulators and HTA committees will similarly need to adjust if they are to continue to sit. These committees, like research ethics committees, will also be under-resourced as many members are clinicians, public health or allied health professionals. When committees do meet, they will need to be quorate and may require in camera sessions because of confidential discussions regarding price. There has been quick uptake of videoconferencing software, but there are some concerns regarding the security of these platforms [23]. Additionally, it may be that there is less patient participation in these virtual HTA committees, those with certain medical conditions and possibly individuals without computer skills may not be able to participate in the same manner that they would when in a face-to-face meeting.

The FDA and EMA have both provided guidance to sponsors regarding ongoing trials and the initiation of new trials, but it is still too early to understand what these changes will mean when sponsors begin the process of regulatory approval and licencing. One assumes that there will be some leniency: perhaps patient-reported outcome measures will gain favour over clinical outcome measures [24], or the agencies will be more amenable to deviations from published statistical analysis plans and will need to accept alternative statistical analyses [25]. With respect to committee meetings, the FDA are cancelling or postponing all non-essential meetings in April although they have expressed a willingness to using virtual advisory committees [26], while the EMA announced in early March that EMA committees and working parties will be held virtually until the end of April 2020 [27].

Another, more significant, regulatory postponement is the proposal from the European Commission to postpone the enforcement of the Medical Device Regulation (European Union) 2017/745, which was to have been imposed from 26 May, 2020 [28]. The reasoning is that fewer resources are available to implement the regulation, and there is a more urgent need for the industry to focus on tackling COVID-19. Effectively, this means prioritising COVID-19 at the expense of more rigorous requirements on medical devices, including the requirement of more clinical evidence.

HTA agencies are also refocusing their activities to prioritise COVID-19, for example, the National Institute for Health and Care Excellence (NICE) has produced rapid guidelines ($N = 12$ as of mid-April) and evidence summaries. Notably, NICE "were advised cost was not an issue [when producing guidelines] only what's best for the service." (Gillian Leng, NICE Chief Executive, [29]). NICE's fee-based consultancy service to industry has chosen to offer free scientific fast-track advice for companies developing novel diagnostic, therapeutic and digital health technologies for COVID-19 [30]. With respect to other guidance and guidelines, during the pandemic NICE has decided to publish only work that is either therapeutically critical (this includes cancer medicines, except cancer drugs fund reviews and a small number on non-cancer medicines) or that relates to addressing COVID-19 diagnostic or therapeutic interventions, to avoid distracting the National Health Service (NHS) [31]. Like regulatory agencies, HTA committees may also need to accept alternative analytical approaches where, because of COVID-19, there are missing data [32] or censored data [33]. NICE has recently delayed its timelines for their methods and process review (personal e-mail communication), thereby allowing the UK Department of Health and Social Care and NHS England to prioritise their response to COVID-19.

Even when pharmaceutical companies receive regulatory and market access approvals, there may still be delays in

launching technologies. Companies' planned approaches to launch prior to COVID-19 are unlikely to apply in a post-COVID healthcare system. Priorities and methods of working will have changed, and this may include how companies engage with healthcare professionals (current social distancing rules mean this is not in person), and how healthcare professionals engage with patients. Depending on the extent of the pandemic, the way we deliver healthcare could change; there may be a stronger push to deliver care at home and to use digital technologies.

6 Health Technology Assessment for COVID-19 Therapies

It would be amiss to discuss the impact of a pandemic on HTA without discussing the assessment of COVID-19 therapies. While NICE COVID-19 guidelines appear to have been issued devoid of formal economic appraisals, it would be unusual for policy makers to adopt treatments and preventative approaches without assessing both effectiveness and cost effectiveness. Different HTA agencies have different levels of oversight, for example, in Australia and New Zealand, the Pharmaceutical Benefits Advisory Committee and Pharmaceutical Management Agency (PHARMAC), respectively, review both pharmaceuticals and vaccines, but in the UK, NICE reviews pharmaceuticals while the Joint Committee on Vaccination and Immunisation (JCVI) assesses vaccines [34]. This introduces the potential for different agencies to apply different standards to the many COVID-19 interventions; indeed, NICE has different reference cases for public health interventions and health technologies.

Methods aside, policy makers need economic evidence on both costs and outcomes. As of early April, there were 366 COVID-19 studies registered worldwide [35]. A review of several registered clinical trials suggests that few appear to be designed to investigate efficacy [36] and our own search of the European Union Clinical Trials Register (www.clinicaltrialsregister.eu) and ClinicalTrials.gov (www.clinicaltrials.gov) identified no COVID-19 studies that appear to be explicitly collecting resource use, cost or quality-of-life data. Health economists are no strangers to modelling and extrapolating trial data, or making and testing assumptions to undertake HTAs (see [37] for a COVID-19 modelling example); but assumptions should never replace the opportunity to collect actual data, particularly to go beyond clinical outcomes of hospitalisations to consider quality-adjusted life-years (QALYs). Early HTA can inform research and development during the initial stages of clinical research — potentially important with so many competing treatments being trialled — and help address uncertainty [38]. It is likely that such therapies will be fast tracked through any HTA process (and thereby delay other topics), but faster appraisal may mean drugs are approved that are neither clinically nor cost effective, or there is a greater chance of a negative recommendation as the committee considers there are too many uncertainties.

It is also worth positing whether these COVID-19 prevention, testing or treatment strategies will be assessed against the usual cost-effectiveness threshold? Current prevention and testing strategies have not been evaluated to this degree (as far as we are aware), and perhaps the middle of a pandemic is not the best time to debate the value of life. What has become evident is that there are clear opportunity costs of addressing the COVID-19 pandemic, in terms of diverting resources from other diseases with undocumented consequences [39].

7 Adapting to a New Normal

When we do return to a 'new normal', an obvious question to ask is whether healthcare systems will have money to make decisions about whether to adopt health technologies. The majority of investment in COVID-19 has to date been new funding, i.e. not at the expense of the current healthcare budget although arguably at the expense of the wider economy. This and the various stimulus packages that have been announced globally are the result of quantitative easing and/or government borrowing. In the short run, these stimulus packages will allow the economy and healthcare systems to function, but a global recession is highly likely, and consumer and business confidence will take a hit. Venture capital funding may be difficult to secure, which will add challenges for the life sciences sector bringing new innovations to market.

Governments often adopt HTA to support cost containment during economic crises to aid financial sustainability [40]. Therefore, a well-functioning HTA system (as many countries have) will be critical. What is not clear is whether governments will constrain the budgets of HTA agencies, which would be reflected in part in them facing a lower threshold of cost effectiveness. Given the perceived inflexibility across countries of the threshold [41, 42], and the disconnect between adoption decisions and budget impact (for example, NICE does not face the opportunity cost of its decisions, NHS England does [43]) it may be that HTA needs to focus its efforts on 'technology management' rather than 'technology adoption' and evaluate divesting in inefficient services or low-value healthcare [44]. Alternatively, HTA agencies in response to financial uncertainty may become more risk averse, which could be further magnified given the evidence base they will evaluate may be more uncertain because of the current disruption to clinical trials. It may be that faced with such a situation, HTA agencies and other healthcare funders will rely more heavily on other coverage

decision approaches such as risk sharing arrangements or managed access schemes [45]. These innovative market access policies may be accompanied by innovations in pricing arrangements, including outcome-based payments [46], thereby promoting patient access despite the uncertainty in the evidence base and an aversion to risk at times of financial crisis [47].

There are many news articles on how COVID-19 will change the world [48], including that we cannot go back to normal [49]. Undoubtedly this is true. Our healthcare systems are changing rapidly, and our means of undertaking assessments of value will also need to change. HTA is not immune to COVID-19, but it can and will adapt.

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