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## The Duty to Support Learning Health Systems: A Broad Rather than a Narrow Interpretation

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As of October 23, 2020, almost 42 million cases of COVID-19 have been reported globally (COVID-19 Situation Update Worldwide 2020). Although many different treatments have been applied in infected people, thus far, evidence on the actual benefit of these treatments is lacking (Pan et al. 2020). The need to rearrange the health care system in such a way as to improve the evidence on treatment for people infected with SARS-CoV-2 and to maximize the system's potential to create meaningful outcomes has been well-recognized (North, Dougan, and Sacks 2020). At the same time, uncertainty and disagreement about what is best for patients is a well-known and wide-spread phenomenon in medicine, not only in times of a pandemic with a novel disease (Garrow 2007; Prasad, Cifu, and Ioannidis 2012). In order to improve the evidence-base for people with SARS-CoV-2 infections, but also for patients with other diseases, Alex John London (2021) defends a Duty to Support Learning Health Systems: "When experts disagree or are uncertain about the best means of preventing, diagnosing or treating sickness, injury or disease, medical professionals have a duty to support, and not to undermine, health systems that conduct scientifically sound and socially valuable studies in a timely manner in order to eliminate or substantially reduce this conflict or uncertainty without compromising respect for the rights and interests of study participants" [our italics] (London 2021, 10). Although we are sympathetic to a duty to support Learning Health Systems as defended by London, we think that the duty needs further interpretation and may be sharpened in order to be meaningful.

As we see it, London has implicitly formulated a *narrow* conception of this duty. First, the duty is addressed

solely at medical professionals. For example, he writes that it is the medical professional who should start "scientifically sound and socially valuable research" (10) when there is uncertainty and disagreement about the treatment of novel conditions. Although it is not clear which experts precisely fall into this category, the literature on learning health systems informs us that a meaningful rearrangement of the health care system not only asks of medical professionals to support this system but also of others, running from boards of directors, research ethics committees, patients themselves and society at large (Faden et al. 2013; Wouters et al. 2020). Moreover, medical professionals are not supposed to work in isolation but should discuss the need and best way to solve these uncertainties and disagreements with other professionals and societal stakeholders before they start their studies. Furthermore, medical professionals need a well-functioning research infrastructure, including the funds to carry out their research, a proper data management system and sufficient and qualified personnel such as research nurses. Moreover, in order to establish a Learning Health System, research ethics committees should acknowledge the increase of research embedded in a health care system where care and research practices cannot always be easily distinguished and have a mechanism in place to review protocols for Learning Health Systems (Faden et al. 2013; Wouters et al. 2020). Furthermore, patients and the public need to be engaged in order to create meaningful research questions and to be informed that their data may be used for large scale research projects (Faden et al. 2013; Wouters et al. 2020).

Second, from the paper as a whole it becomes clear that London seems most interested in using randomized clinical trials (RCTs) to solve states of uncertainty or

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disputes in health knowledge. For example, he states that “when informed medical experts are uncertain about which care is optimal, or they have definitive but conflicting preferences for different interventions, RCTs represent a way of providing access to medical interventions under conditions that support reliable inference about the relative clinical merits of those interventions” (London 2021, 10). Furthermore, there is no mentioning of other research methods that can be deployed in an LHS.

We agree that the use of RCTs in a pandemic and beyond is essential, in particular for obtaining evidence about novel interventions or about existing medications for novel indications. But to solve every state of uncertainty with an RCT would be virtually impossible and is not always ideal. First, there are many types of research that do not need the RCT as a method, but still are essential for progress in a health system, for example, diagnostic or prognostic research, or the generation of hypotheses (Grobbee and Hoes 2014). Second, whether or not RCTs are the best means to solve disputes or states of uncertainty also depends on the type of intervention of interest. A completely new intervention may require an RCT to study its effectiveness and (short-term) safety as compared to care as usual; however, in the case of two interventions that have already been applied in clinical practice and where allocation of interventions is at random and not based on patient characteristics, a comparison of both interventions based on observational data may be sufficiently valid to inform clinical practice (Grobbee and Hoes 2014). Third, despite their methodological challenges (such as selection bias and confounding) observational studies generally have longer follow-up, allowing for assessment of long-term efficacy and safety, larger sample size, more generalizable eligibility criteria, and hard outcomes than RCTs (Concato et al. 2000). As such, evidence from observational research can 1) complement evidence from RCTs, 2) serve for hypothesis generation, and 3) serve as an intermediate basis for clinical decision making until evidence from RCTs becomes available (Halperin et al. 2016). Fourth, the successful use of RCTs in a health system is dependent upon how well the health system itself is arranged to create meaningful and timely outcomes. For example, the so-called “Trials within Cohorts [TwiCs]” design where clinical trials are embedded in cohorts has been created with the aim to improve recruitment rates and to enable treatment comparisons (Relton et al. 2010).

In sum, it is the organization of the health care system that needs to be transformed and let RCTs flourish optimally, provided that they are the best means to resolve

knowledge conflicts. Already in 2007, the Institute of Medicine called upon health care leaders to transform their systems into learning health care systems (Olsen, Dara, and Michael McGinnis 2007). Thus far, however, real examples of implementations of Learning Healthcare Systems have remained scarce, despite their theoretical potential (Budrionis and Bellika 2016).

A strong Learning Health System (LHS) is essential for optimally designed and appropriately conducted RCTs. Observational data can be used as a starting point for generating hypotheses, and for a first exploration of the effectiveness and safety of interventions. Subsequently, RCTs can be used to study research questions in a more robust manner. In regard to the COVID-19 pandemic, we have seen the importance of both international collaboration and having a structure in place that is able to embed RCTs, for example, by using adaptive platform designs such as the WHO SOLIDARITY trial (World Health Organization 2020). Currently, the SOLIDARITY Trial “is ongoing in 30 countries among the 43 countries that have approvals to begin recruiting. Overall, 116 countries in all 6 WHO regions have joined or expressed an interest in joining the trial” (World Health Organization 2020). Readiness and preparedness of health systems for such a way of learning seems essential to create progress in a pandemic. Moreover, during the outbreak of the COVID-19 pandemic (and other disease outbreaks) we have seen that time is simply lacking to afford the conduct of a robust RCT, and treatment decisions need to be taken on observational data only. The World Health Organization (WHO) emphasizes the importance of monitoring emergency use of unregistered and experimental interventions (MEURI) in a disease outbreak (World Health Organization 2018). According to WHO, physicians overseeing MEURI have the same moral obligation to collect all scientifically relevant data on the safety and efficacy of the intervention as researchers who perform a clinical trial (World Health Organization 2018). Arguably, a health system that is prepared for proper registration of characteristics and outcomes of patients treated with experimental interventions could facilitate assessment of efficacy and safety and is essential to improve the evidence base for these interventions. Eventually, in a preexistent LHS the infrastructure for data collection in this way would have already been in place.

Therefore, we defend a *broad* conception of the Duty to Support Learning Health Systems which is in line with the IOM’s interpretation of an LHS (Olsen, Dara, and Michael McGinnis 2007). We argue that this duty implies: *Relevant stakeholders of Health*

System, including community representatives, patients, boards of directors, nurses, physicians, societal stakeholders, funders, research ethics committees and researchers have a duty to rearrange their health care system in such a way that this system systematically learns from the collection, storage and use of routinely collected data in order to improve the evidence base of medicine. The infrastructure that facilitates learning from routinely collected data may be used to embed RCTs that may help us to assess efficacy and safety of interventions, but can also be used to address diagnostic and prognostic research questions by means of cohort studies. In addition, this duty includes improvements in management (infrastructure), uniform way of collecting data, patient engagement and ethical oversight systems.

In such a system, in which data are already routinely collected and studied, MEURI data can easily be merged while awaiting the conduct of robust RCTs, including adaptive platform trials, but the data can also be used to discern promising interventions from interventions that are deemed to fail. In that way, many burdensome and costly RCTs can also be prevented.

## DISCLOSURE STATEMENT

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